

Deuterium isotope effects on C-13 chemical shifts as a tool to determine tautomerism and structural features in intramolecular hydrogen bonded systems

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Deuterium isotope effects on ^{13}C chemical shifts as a tool to determine tautomerism and structural features in intramolecular hydrogen bonded systems.

Ph.D. thesis

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Roskilde University, Denmark 1997



Resumé

En række forbindelser indeholdende intramolekylære hydrogenbindinger er studeret ved hjælp af deuterium isotopeffekter primært på ^{13}C kemiske skift, men også på ^{19}F kemiske skift.

Deuterium isotopeffekter på kemiske skift har vist sig anvendelige til beskrivelse af intramolekylære hydrogenbindingssystemer (og er ikke kun en parameter der er proportional med det kemiske skift). Deuterium isotopeffekter på ^{13}C kemiske skift har vist at kunne klarlægge svækkelser af hydrogenbindinger på grund af sterisk hindring og styrkelse af disse grundet sterisk kompression. Når to donorer konkurrerer om en acceptor er det vist at den intramolekylære hydrogenbinding svækkes.

Udskiftning af hydrogen med deuterium i en intramolekylær hydrogenbinding forårsager en forskydning af ligevægten. Dette er observeret for både tautomer ligevægte og konformations ligevægte.

Deuterium isotopeffekter på ^{13}C kemiske skift er benyttet til at løse strukturelle problemer så som, konformationen af den mindst befolkede form af 3,5-diacetyltetrahydropyran-2,4,6-trion og dynamikken af 1-acetyl-2-hydroxy-3-nitro-6-methoxybenzen.

Deuterium isotopeffekter på ^{13}C kemiske skift er ligeledes vist at være en god indikator for tautomeri. For enoliserede β -diketoner er perturbationen af den tautomere ligevægt således vist at afhænge af ligevægtskonstanten. Enoliske β -ketoamider, enoliske 1,3-indandione thioamider og enoliske 5-acyl 1,3-dimethylbarbitur syrer er fundet at være tautomere.

Isotopeffekter på ^{13}C kemiske skift målt for nogle enoliske 5-acyl meldrum syrer antyder at disse er tautomere, hvilket er usædvanligt idet en ester karbonyl gruppe i β -ketoestere ikke enoliserer.

Abstract

A range of compounds forming intramolecular hydrogen bonds are studied by means of deuterium isotope effects, primarily on ^{13}C chemical shifts but also on ^{19}F chemical shifts. Deuterium isotope effects on chemical shifts are shown to be useful descriptors of intramolecular hydrogen bonded systems, (and not only a parameter proportional to the chemical shifts).

It is shown that deuterium isotope effects on ^{13}C chemical shifts can reveal weakening of an intramolecular hydrogen bond due to steric hindrance and strengthening due to steric compression. Two donors competing for one acceptor are shown to weaken the intramolecular hydrogen bond.

Exchanging hydrogen for deuterium in an intramolecular hydrogen bond is seen to perturb the equilibrium. This is observed for both tautomeric and conformational equilibria.

Solving structural problems like the conformations of the minor form of 3,5-diacetyltetrahydropyran-2,4,6-trione, and the dynamic of 1-acetyl-2-hydroxy-3-nitro-6-methoxybenzene is greatly helped by means of deuterium isotope effects on ^{13}C chemical shifts.

Deuterium isotope effects on ^{13}C chemical shifts is shown to be a probe for tautomerism. For enolic β -diketones, the perturbations of the tautomeric equilibrium are shown to depend on the equilibrium constant. Enolic β -ketoamides, enolic 1,3-indandiones thioamides and enolic 5-acyl 1,3-dimethylbarbituric acids are here by shown to be tautomeric. The isotope effects on ^{13}C chemical shifts measured for some enolic 5-acyl meldrum acids suggest that these are tautomeric, which is unusual as the ester moiety in enolic β -ketoesters are not on the enolic form.

Preface

From the time period of November 1, 1992 through marts 1, 1996 I was employed as a research and teaching assistant at the department of Life Sciences and Chemistry, Roskilde University, interrupted by five months of military service. I stayed one month in Kent, Ohio, in the summer of 1995 visiting Professor Kenneth K. Laali at Kent State University. The work with Professor Kenneth K. Laali, concerning direct fluorination and protonation of polyaromatic compounds, is not included in this thesis. The financial support by NATO (CRG930113) for this stay is greatly appreciated.

Financial support from the Danish Natural Science Research Council, in the period March 1, 1996 through to March 1, 1997, made it possible to stay at Northeastern University, Boston, visiting Professor David A. Forsyth for six months. In Boston was I involved in two projects, one concerning synthesis of dihydro-dialkyl- benzenes, naphthalenes and anthracenes, and deuterium isotope studies of these, and the other concerning dynamic NMR and molecular mechanics studies of substituted 3-pyrryl-2-oxo-oxolan, both of which is not part of this thesis.

An update of the important observations and trends observed by deuterium isotope effects on intramolecular hydrogen bonded systems is given in the introduction. It consists of sections introducing hydrogen bonds, isotope effects and the basic theory for these effects. The result section consists of a summary of the ten papers included in the appendix. Examples of results show how deuterium isotope effects can be used to determine tautomerism and structural features in intramolecular hydrogen bonded system. The report is best read in conjugations with the papers in the back, but it is my intention that it can be read as a separate report.

Several people have helped and inspired me during my studies, I especially want to thank: Poul Erik Hansen, Anne Lise Gudmundsson, Fritz Duus, Morten Christoffersen and Morten Langgård, Department of Life Sciences and Chemistry, Roskilde University. David A. Forsyth and John Hanley, Department of Chemistry, Northeastern University, Boston. Kenneth K. Laali, Department of Chemistry, Kent State University, Ohio. Donka Kh. Zheglova, Department of Organic Chemistry, University of Sofia, Bulgaria.

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1. List of Papers

- I. Poul Erik Hansen, Morten Christoffersen and Simon Bolvig, Variable-Temperature NMR Studies of 2,6-dihydroxy Acylaromatic Compounds. Deuterium Isotope Effects on Chemical Shifts, Isotopic Perturbation of Equilibrium and Barriers to Rotation. *Magn. Reson. Chem.* **31**, 893-902 (1993).
- II. Poul Erik Hansen, Solveig N. Ibsen, Tina Kristensen and Simon Bolvig, Deuterium and ^{18}O Isotope Effects on ^{13}C Chemical Shifts of Sterically hindered and/or Intramolecularly Hydrogen-Bonded *o*-Hydroxy Acyl Aromatics. *Magn. Reson. Chem.* **32**, 399-408 (1994).
- III. P.E. Hansen, S. Bolvig, F. Duus, M.V. Petrova, R. Kawecki, R. Krajewski and L. Kozerski, Deuterium Isotope Effects on ^{13}C Chemical Shifts of Intramolecularly Hydrogen-Bonded Olefins, *Magn. Reson. Chem.* **33**, 621-631 (1995).
- IV. Poul Erik Hansen, Simon Bolvig and Thomas Kappe, Intramolecular hydrogen bonding and tautomerism of acylpyran-2,4-diones, -2,4,6-triones and acylpyridinediones and benzannelated derivatives. Deuterium isotope effects on ^{13}C NMR chemical shifts, *J. Chem. Soc. Perkin Trans. II*, 1901-1907 (1995).
- V. Simon Bolvig and Poul Erik Hansen, Deuterium-Induced Isotope effects on ^{13}C Chemical Shifts as a Probe for Tautomerism in Enolic β -Diketones. *Magn. Reson. Chem.* **34**, 467-478 (1996).
- VI. Poul Erik Hansen, Fritz Duus, Simon Bolvig and Tadeusz S. Jagodzinski, Intramolecular hydrogen bonding of the enol forms of β -ketoamides and β -ketothioamides. Deuterium isotope effects on ^{13}C chemical shifts. *J. Mol. Struct.* **378**, 45-59 (1996).

- VII. Donka Kh. Zheglova, Daniel G. Genov, Simon Bolvig and Poul Erik Hansen, Deuterium Isotope Effects on ^{13}C Chemical Shifts of Enaminones. *Acta Chem. Scand.*, submitted.
- VIII. Poul Erik Hansen, Simon Bolvig, Agnes Buvári-Barcza and Antonin Lycka, Long Range Intrinsic and Equilibrium Deuterium Isotope Effects on ^{19}F Chemical Shifts. *Acta Chem. Scand.*, in press.
- IX. Poul Erik Hansen and Simon Bolvig, Deuterium Isotope Effects on ^{13}C Chemical Shifts of *o*-Hydroxy Acylaromatics. Intramolecular Hydrogen Bonding. *Magn. Reson. Chem.*, in press.
- X. Simon Bolvig, Fritz Duus and Poul Erik Hansen, Tautomerism of Enolic Triacetylmethane 2-Acyl 1,3-cycloalkanediones, 5-acyl Meldrums acids and 5-acyl 1,3-Dimethylbarbituric Acids studied by means of Deuterium Isotope Effects on ^{13}C Chemical Shifts. *Magn. Reson. Chem.*, To be submitted.

2. Introduction

Hydrogen bonding and proton transfer reactions are important for the structure and reactivity of many organic compounds and biomolecules such as carbohydrates, hormones and enzymes.¹⁻³ An additional motivation for studying hydrogen bonds is the importance of these and proton transfer reactions for living systems.

Since the first report on isotope effects on nuclear shielding was published in 1953 by T. F. Wimett,⁴ has hydrogen substitution for deuterium in organic compounds been a very useful tool for organic chemists to profound understanding of the structural features and dynamics of organic compounds.

The hydrogen in a hydrogen bond can easily be exchanged with deuterium. Introducing deuterium is a change in mass for the atom between the two hetero atoms constituting the hydrogen bond. When studying hydrogen bonds this change is very fundamental. This makes deuterium isotope effects on chemical shifts a very usable technique to study hydrogen bonds. Hydrogen bonds can be divided into two main categories, intermolecular hydrogen bonds and intramolecular hydrogen bonds. This present work deals with intramolecular hydrogen bonds. Hydrogen bonds as a subject are reviewed by Emsley (1984),⁵ Hibbert and Emsley (1990),⁶ and Dziembowska (1994)² published a review specifically concerning intramolecular hydrogen bonding. These reviews briefly discuss deuterium isotope effects on chemical shifts. Isotope effects on nuclear shielding and equilibrium isotope effects have been reviewed in details by Forsyth (1984),⁷ Siehl (1987)⁸ and Hansen (1983),⁹ (1988).¹⁰ The aspect of isotope effects on nuclear shielding and equilibrium isotope effects in intramolecular hydrogen bonded systems are discussed in the three latter.

2.1 Hydrogen bond

A hydrogen bond is often represented as $X-H\cdots Y$, where X and Y are hetero atoms, (N, O or S). In this description hydrogen is covalently bonded to X and hydrogen bonded to Y. Intramolecular hydrogen bonded compounds are divided into two groups, those with a localized hydrogen bond (figure 1A), and those in which the hydrogen bonds are a part of a

tautomeric system (figure 2). In the localized hydrogen bond system a mechanism designated Resonance Assisted Hydrogen Bond (RAHB) (figure 1B) is shown to be important.^{11,12} The formal partial charge on the oxygen is equalized by a shift in the average proton position, so the charge is reduced. The shift in the average proton position makes the hydrogen bond shorter, and hereby strengthens the hydrogen bond.

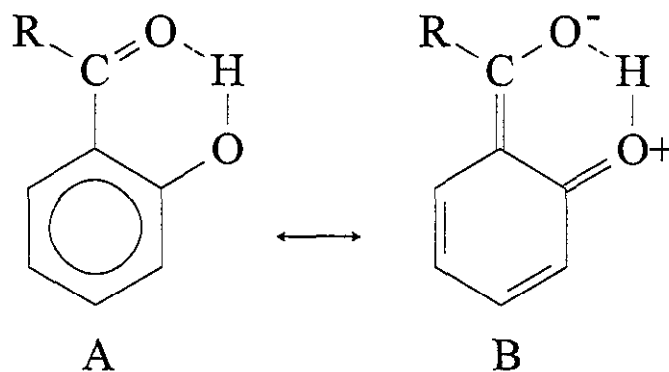


Figure 1. A: Localized hydrogen bond in 2-hydroxy acyl aromatic B: Resonance Assisted Hydrogen Bond (RAHB).

The enolic β -diketone system has been subject to an animated discussion concerning the structure and dynamic.^{11,13-36} It has been argued that the enolic β -diketone system is best described as a symmetrical structure,^{14,15} $R = R''$, (figure 2C). Present, it is argued that the system is best described as a tautomeric equilibrium between the two structures A and B^{8,16-18,23,25,35,37-40} (figure 2A,B).

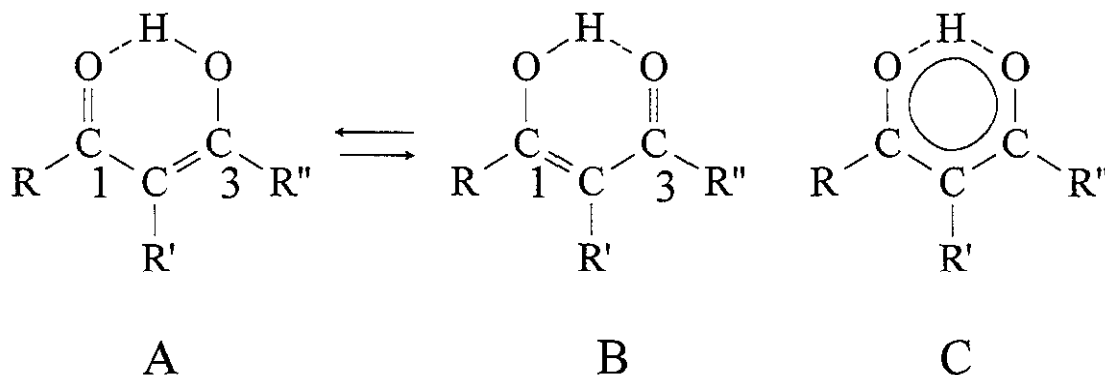


Figure 2. A and B: Tautomeric equilibrium for enolic β -diketones C: Symmetrical descriptions of enolic β -diketones.

NMR-spectroscopy,^{8,17,25,34} microwave spectroscopy,^{37,38} infrared spectroscopy,^{35,39,40} and theoretical calculations^{25,40} have shown that the enolic β -diketone system is a tautomeric system between A and B. This statement is generally accepted today. The symmetric structure (figure 2C) can be a transition state, but this is still to be revealed.¹⁹

The hydrogen bond is influenced by the donor/acceptor as well as the double bond character of the intervening bond. Increasing double bond character hereby promotes RAHB.

The potential energy diagram for the localized case is an anharmonic single minimum potential well (figure 3A). For the tautomeric system it is a double minimum potential well, which is symmetric for a degenerated tautomeric system (figure 3B), and asymmetric when the two tautomeric forms are non-identical (figure 3C).

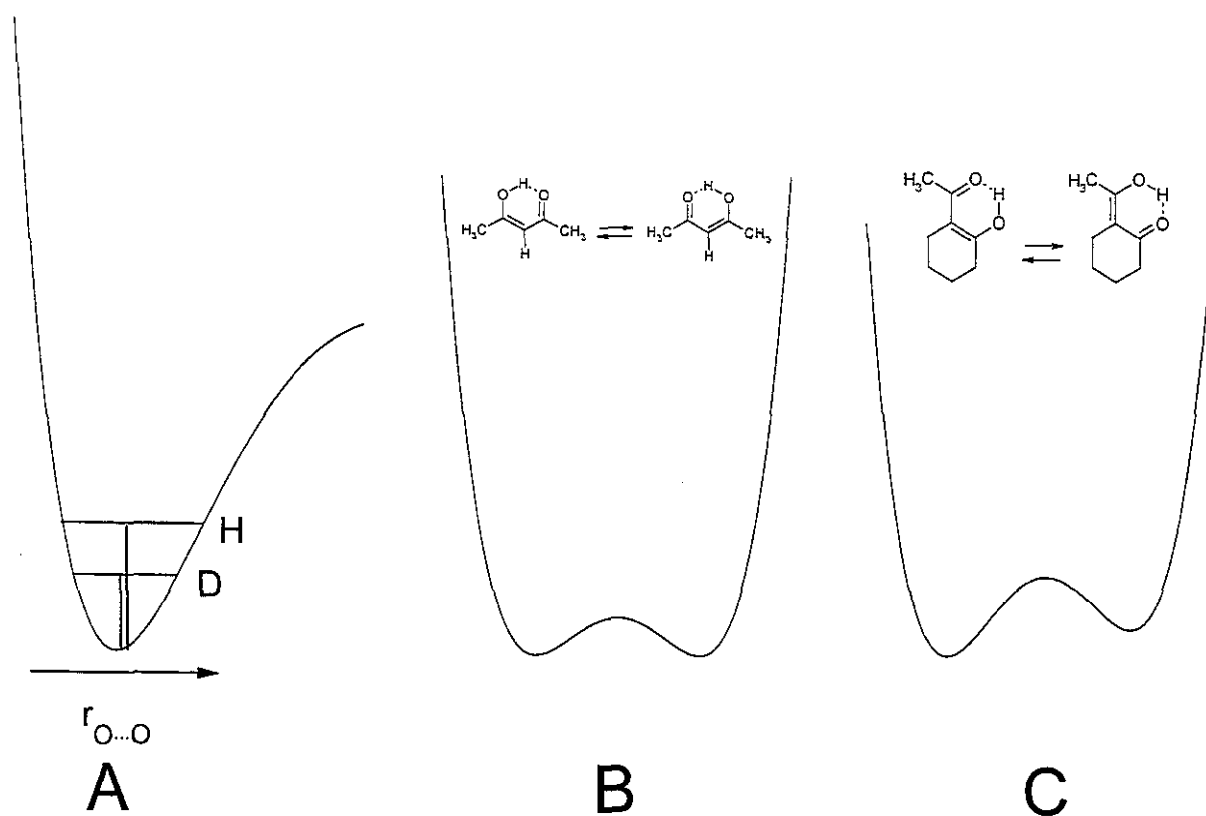


Figure 3. Potential energy diagrams. A: Localized hydrogen bonded system B: Symmetric tautomeric system C: Asymmetric tautomeric system. The labelling H and D refer to hydrogen and deuterium, respectively, and the lines mark the averaged bond length (O-H/O-D).

If no other conformational changes are associated with breaking the hydrogen bond, the strength of the bond is identical with the dissociation energy for the hydrogen bond. A conformational change is normally associated, when an intramolecular hydrogen bond is broken. This makes it difficult to directly determine the dissociation energy. The shorter a distance between Y and H or X and Y, the stronger a hydrogen bond, in the $X-H\cdots Y$ representation.^{6,11,31,41-44} These distances are often given as a measure of the hydrogen bond strength. A rule of thumb state for hydrogen bonds like $O-H\cdots O$; the hydrogen bonds are very strong for $d(O\cdots O) < 2.50\text{\AA}$, strong for $2.50\text{\AA} < d(O\cdots O) < 2.65\text{\AA}$ and considered weak for $d(O\cdots O) > 2.65\text{\AA}$.

Usnic acid is an excellent example of these three categories of hydrogen bonds. The hydrogen bond in the B ring is very strong as $d(O\cdots O)$ is $2.40/2.41\text{\AA}$. This system is shown to be tautomeric. The hydrogen bond in the A ring is of the localized type, similar to the substituted 2-hydroxyacetophenone and is strong as $d(O\cdots O)$ is $2.54/2.53\text{\AA}$. The hydrogen bond between the A ring and the B ring forms a seven-membered ring. Hydrogen bonds in a seven-membered ring are normally weak which is verified by the $d(O\cdots O)$ of $2.66/2.69\text{\AA}$.

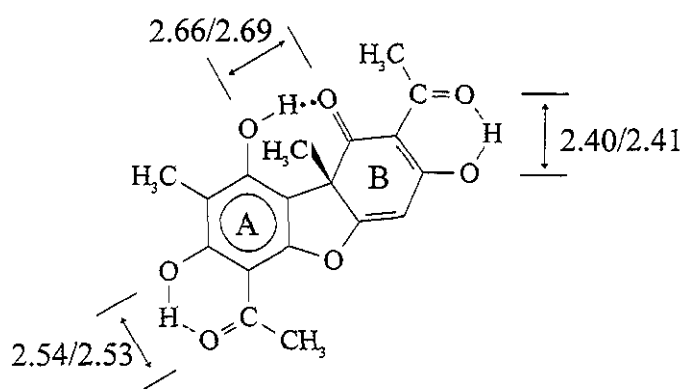


Figure 4. The hydrogen bond length of usnic acid,⁴⁵ (in \AA) determined by x-ray diffraction. The two sets of data refer to two different usnic acids molecule in the unit cell.

In 1961 Gränacher⁴⁶ established a linear correlation between the O^1H chemical shift for intramolecular hydrogen bonded phenols and the observed stretching frequency. A similar correlation was found by Allan and Reeves in 1962.⁴⁷ In 1975 Schaefer,⁴⁸ based on the work by Gränacher⁴⁶ and Allan and Reeves,⁴⁷ found a correlation (eq. 1) between the hydrogen

bond energy (E ; kJ/mol) and the change in chemical shifts relatively to phenol ($\Delta\delta$; ppm)

$$\Delta\delta = -0.4 \pm 0.2 E \quad (\text{eq. 1})$$

From this equation the hydrogen bond energy for 2-hydroxybenzaldehyde can be estimated to 30.1 ± 0.8 kJ/mol. The strength of the hydrogen bond in 2-hydroxybenzaldehyde can from the classifications of Dziembowska² be classified between weak and medium. Dziembowska² classified the intramolecular hydrogen bond as weak ≤ 30 kJ/mol, medium 30 - 70 kJ/mol and strong ≥ 70 kJ/mol.

In intramolecular hydrogen bonded systems, the ^{17}O chemical shifts, are shown to depend primarily on intramolecular hydrogen bonds strength.⁴⁹ Substituent and steric effects have a minor effect which is one order of magnitude smaller.⁴⁹ The change in carbonyl ^{17}O chemical shifts induced by hydrogen bond is linearly correlated with both ^{17}O and ^1H chemical shifts of the OH group.⁴⁹ ^{17}O chemical shifts are therefor a tool for determination of the hydrogen bond strength in intramolecular hydrogen bonded systems.

2.2 Isotope effects

Isotope effects on nuclear shielding are observed when a nucleus is exchanged with an isotope of a different mass. These effects are divided into two categories, primary and secondary isotope effects. The abbreviation PIE and SIE are often used for the primary and secondary isotope effects, respectively. The primary isotope effects are the difference in nuclear shielding of two isotopes and are defined as:

$$\Delta\delta(\text{L,H}) = \delta\text{L} - \delta\text{H} \quad (\text{eq. 2})$$

δL is the chemical shift of the light isotope, and δH the chemical shift of the heavier isotope. This type of isotope effect can only be measured for elements that have two NMR active isotopes.

The secondary isotope effects on nuclear shielding are the difference in the shielding caused by two different isotopes upon the observed nucleus, in two different isotopomers. The secondary isotope effects are defined as:

$$^n\Delta Y(\text{H}) = \delta Y(\text{L}) - \delta Y(\text{H}) \quad (\text{eq. 3})$$

n denotes the number of bonds between the observed nucleus and the site of the isotope exchange. $\delta Y(\text{L})$ and $\delta Y(\text{H})$ is the nuclear shielding of the observed nucleus, Y , substituted

with a lighter and heavier isotope, respectively. This definition will be used in the present work. In some work the opposite sign notation is used.

The secondary isotope effects can be divided into two categories, intrinsic isotope effects and equilibrium isotope effects. Both of which are observed as the difference in resonances, as given in eq. 3. Intrinsic and equilibrium isotope effects differ in their origin and the difference is observed from the magnitude-, signs- and temperature dependence of the isotope effects.

Intrinsic isotope effects are observed in static, none equilibrating species, described as an anharmonic single minimum potential energy diagram (figure 3A). The equilibrium isotope effects occur when the equilibrium is perturbed by the isotope substitution. This is observed for systems described as a double minimum potential energy diagram (figure 3C).

A sample is an isomeric mixture when the labelling is less than 100%. If isotopomers are non-exchanging or the exchange is slow, compared to the characteristic NMR time, ($1/\Delta\nu$), the resonating nuclei in both the labelled and the unlabelled compounds will be observed. The intensities of resonances is proportional with the ration of the isotopomers.

The present work deals with deuterium isotope effects on ^{13}C nuclear shielding and to some extend also on ^1H and ^{19}F nuclear shielding. L = Hydrogen and H = Deuterium in eq. 3 and Y are either ^{13}C , ^1H or ^{19}F . The notation $^2\Delta\text{C}(\text{OD})$, means two bond isotope effects on ^{13}C chemical shifts due to deuteration at oxygen.

2.3 Basic theory of isotope effects

The theory of isotope effects in chemical reactions and on the reaction rates are well established, and are presented in details in several books.⁵⁰⁻⁵³ The theory of isotope effects on nuclear shielding over one bond are established.⁵⁴⁻⁵⁶ However a full theoretical treatment of long range isotope effects is still to be revealed. Jameson⁵⁴ has shown that the term including the bond displacement at the site of exchange is the dominating for long range isotope effects. This paragraph will present some theoretical aspects of isotope effects on nuclear shielding and isotope effects on chemical equilibrium.

2.3.1 Intrinsic isotope effects

The formalism concerning isotope effects on nuclear shielding describes small changes in molecular geometry and molecular wave functions due to vibrational averaging, which is closely related to the formalism for temperature dependence of nuclear shielding.^{55,57-59}

The isotope effects on nuclear shielding are rotational and vibrational in origin. Only the vibrational term is important in larger molecules which is slowly rotating. The observed nuclear magnetic shielding (σ) is the average shielding over the contributing vibrational and rotational states. Substituting an atom for its heavier isotope results in a lower vibrational energy, and a shorter average bond length.^{54,60,61}

The Born-Oppenheimer approximation states that all isotopomers have the same potential surface. Within the Born-Oppenheimer approximation, an isotopomer with a lower vibrational energy in an anharmonic potential, averages to a different geometry (Figure 3A).

2.3.2 Intrinsic isotope effects over one bond

According to Jameson,⁵⁴ the mass induced change on the nuclear shielding, $\langle\sigma\rangle - \langle\sigma\rangle^*$, can be expressed as:

$$\langle\sigma\rangle - \langle\sigma\rangle^* = (\partial\sigma/\partial r_1)_e [\langle\Delta r_1\rangle - \langle\Delta r_1\rangle^*] + \text{smaller terms} \quad (\text{eq. 4})$$

where * denotes the heavier isotopomer, Δr_1 is the bond displacement at the site of substitution.

It is shown that the term, including bond displacement at the site of substitution, gives the largest contribution to the isotope over one bond. Terms that include; second and higher derivatives of nuclear shielding, bond angle deformations and derivations of the shielding with respect to the bond angle, shielding change due to the small secondary changes in bond length elsewhere in the molecule, are all small terms. These small terms include changes in the nuclear shielding, for the nuclear in question, due to changes in the conformation elsewhere in the molecule. These conformational changes are induced by isotope substitution one bond away from the nuclear in question.

2.3.3 Intrinsic isotope effects over more than one bond

Jameson⁵⁴ showed, that isotope effects over more than one bond is a property of the electronic transmission path from the site of substitution to the nucleus in question. For isotope effects

over two or more bonds, secondary factors have to be considered. These factors are the change in shielding due to a change in bond length in a remote bond caused by a substitution elsewhere in the molecule.

When a carbon nucleus in C-O-H is considered, the primary dynamic factor is the change in the O-H(D) bond length upon substitution of H by D, $\langle r_{OH} \rangle_{COD} - \langle r_{OH} \rangle_{COH}$. The secondary dynamic factor is the much smaller change in C-O bond length upon substitution of H by D, $\langle r_{CO} \rangle_{COD} - \langle r_{CO} \rangle_{COH}$. The primary electronic factor is the change in shielding due to the change in the bond length C-O upon substitution of H by D, $(\partial\sigma^C/\partial r_{CO})_e$. The secondary electronic factor is the change in shielding on the carbon nucleus due to the change in the O-H bond length upon substitution of H by D, $(\partial\sigma^C/\partial r_{OH})_e$.

For 2-bond isotope effect the dominating terms on a carbon nuclei can be expressed as:

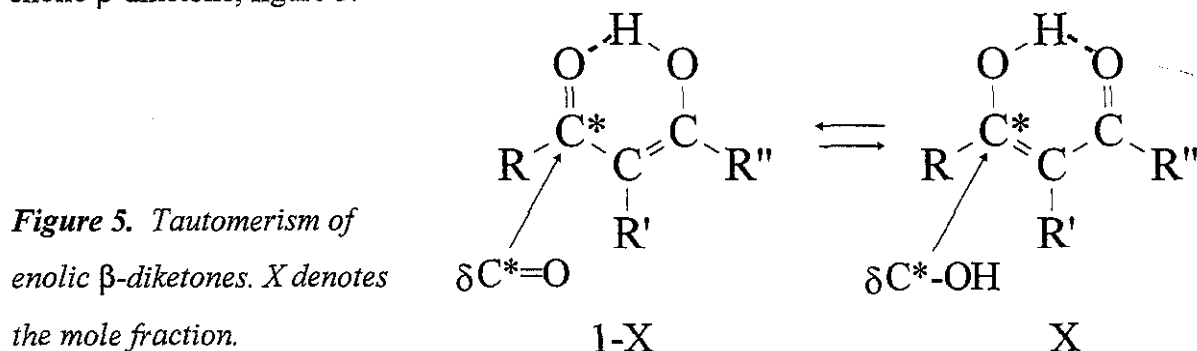
$$\langle \sigma^C \rangle - \langle \sigma^C \rangle^* = ((\partial\sigma^C/\partial r_{CO})_e \times (\langle r_{CO} \rangle_{COD} - \langle r_{CO} \rangle_{COH})) + ((\partial\sigma^C/\partial r_{OH})_e \times (\langle r_{OH} \rangle_{COD} - \langle r_{OH} \rangle_{COH})) \quad (\text{eq. 5})$$

Even for long-range isotope shifts are there according to Jameson,⁵⁴ evidence that terms including $\langle r_{OH} \rangle_{COD} - \langle r_{OH} \rangle_{COH}$ are dominant compared to terms including $\langle r_{CO} \rangle_{COD} - \langle r_{CO} \rangle_{COH}$. From this follows that the major contribution to the isotope effect on nuclear shielding comes from the change in bond length at the site of exchange.

2.3.4 Equilibrium isotope effects

An equilibrium isotope effect is observed when isotopomeric compounds shows different equilibrium constants. To observe the equilibrium isotope effects by means of NMR chemical shifts, the chemical shifts for the nuclear in question must differ in the two interchanging isotopomers.

The contributions to the equilibrium isotope effects are exemplified for a non-symmetric enolic β -diketone, figure 5.



The observed chemical shift, $\delta_{\text{obs}}\text{C}^*(\text{H})$, is a weighted average of the two separate chemical shifts, $\delta\text{C}^*=\text{O}(\text{H})$ and $\delta\text{C}^*-\text{OH}$. The observed chemical shift can be expressed as:

$$\delta_{\text{obs}}\text{C}^*(\text{H}) = X \times \delta\text{C}^*-\text{OH} + (1-X) \times \delta\text{C}^*=\text{O}(\text{H}) \quad (\text{eq. 6})$$

X denotes the molar fraction. When H is exchanged by D, the observed chemical shift, $\delta_{\text{obs}}\text{C}^*(\text{D})$, can be expressed as:

$$\delta_{\text{obs}}\text{C}^*(\text{D}) = (X - \Delta X_{\text{D}}) \times \delta\text{C}^*-\text{OD} + (1 - (X - \Delta X_{\text{D}})) \times \delta\text{C}^*=\text{O}(\text{D}) \quad (\text{eq. 7})$$

ΔX_{D} denotes the change in the molar fraction, when hydrogen is exchanged with deuterium.

The observed isotope effect, $\Delta\text{C}^*(\text{D})_{\text{obs}}$, is $\delta_{\text{obs}}\text{C}^*(\text{H}) - \delta_{\text{obs}}\text{C}^*(\text{D})$, which can be rationalised to:

$$\Delta\text{C}^*(\text{D})_{\text{obs}} = X \times {}^2\Delta\text{C}^*-\text{O}(\text{D}) + (1-X) \times {}^4\Delta\text{C}^*=\text{O}(\text{D}) + \Delta X_{\text{D}} \times (\delta\text{C}^*=\text{O}(\text{H}) - \delta\text{C}^*-\text{OH}) \quad (\text{eq. 8})$$

Where the contributions from the terms $(\Delta X_{\text{D}} \times {}^2\Delta\text{C}^*-\text{O}(\text{D}))$ and $(\Delta X_{\text{D}} \times {}^4\Delta\text{C}^*=\text{O}(\text{D}))$, are very small, and therefore disregarded.

The term, $\Delta X_{\text{D}} \times (\delta\text{C}^*=\text{O}(\text{H}) - \delta\text{C}^*-\text{OH})$, is the contribution from the equilibrium isotope effects to the observed isotope effect. Large perturbation of the equilibrium, large ΔX_{D} , and a large difference in chemical shifts for the nucleus in question, between the two interchanging forms, $(\delta\text{C}^*=\text{O}(\text{H}) - \delta\text{C}^*-\text{OH})$, will increase the equilibrium isotope effects.

$X \times {}^2\Delta\text{C}^*-\text{O}(\text{D}) + (1-X) \times {}^4\Delta\text{C}^*=\text{O}(\text{D})$ is the weighted average of two- and four bond isotope effects for the nucleus in question.

2.4 Deuterium isotope effects on chemical shifts

Deuterium isotope effects on ^{13}C chemical shifts in intramolecular hydrogen bonded systems have been studied.^{2,7-10,12,13,33,62-86} Different types of intramolecular hydrogen bonded systems display isotope effects of different signs and magnitudes figure 6.

The difference in magnitude, sign and temperature sensitivity observed for isotope effects on ^{13}C shifts for structural different compounds (figure 6), suggested that these carries useful structural information.

One bond isotope effects have been shown to be proportional to the ^{13}C chemical shifts.^{17,54,85,87} Two bonds deuterium isotope effects on ^{13}C chemical shifts of non-hydrogen bonded phenols have been correlated with the ^{13}C chemical shifts,⁸² and to some extent also for hydrogen bonded phenols.¹² The question to ask is if the deuterium isotope effect on ^{13}C

chemical shifts just is a parameter proportional to the ^{13}C chemical shifts or if it contains additional information?, as Jameson⁵⁴ pointed out in 1991.

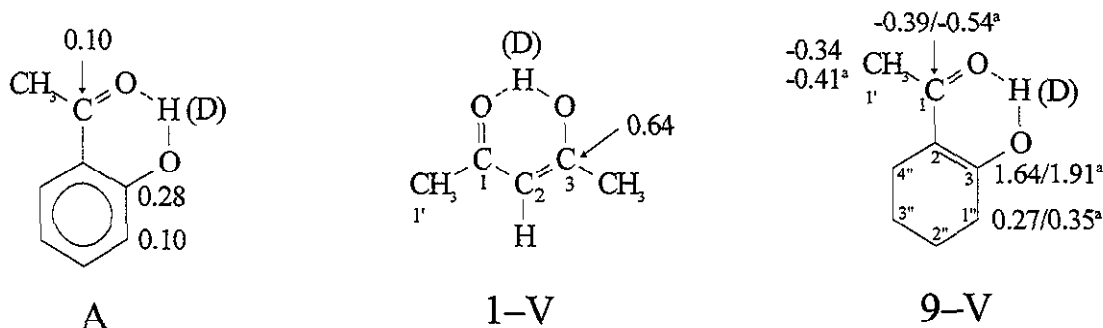


Figure 6. Deuterium isotope effects on ^{13}C chemical shifts measured at 300K for compounds having: A: Localized hydrogen bond, 1-V: Symmetric tautomeric hydrogen bond, 9-V: Asymmetric tautomeric hydrogen bond. (Ref. 65; α : 238K).

The deuterium isotope effects observed when hydrogen is exchanged with deuterium, in an intramolecular hydrogen bonded system, are shown to contain additional information. Enolic keto-enamines can exist in both a Z and an E form, the Z form forms an intramolecular hydrogen bond. Due to the hydrogen bond in the Z form a larger $^2\Delta\text{C}(\text{ND})$ for the Z form, compared with the E form of enamines, is observed.⁸¹

$^2\Delta\text{C}(\text{XD})$, X = O or N is shown to correlate with δXH for aromatic^{12,67,73,78} and for olefins⁸¹ systems. The $^2\Delta\text{C}(\text{OD})$ vs. $\delta(\text{OH})$ for 2-hydroxy- benzaldehydes, acetophenone and alkylbenzoates are shown to fall on different lines, as well as the 4,6 and 3,5 substituted in each series are shown to be different.¹²

Reuben⁷³ has suggested that the hydrogen bond energy, (E), can be estimated from the two bond deuterium isotope effects on ^{13}C chemical shielding; $\ln(^2\Delta\text{C}(\text{D})) = 2.783 + 0.354\text{E}$

2.4.1 Long range isotope effects

$^4\Delta\text{C}(\text{OD})$ and $^5\Delta\text{C}(\text{OD})$ observed for a series of 2-hydroxy acyl aromatic compounds can be correlated with $\delta(\text{OH})$.^{12,78} Isotope effects over six and seven bonds is observed.^{67,74,78} These long-range isotope effects are usually small and of both positive and negative sign. The signs for long-rang isotope effects are suggested to be alternating.^{74,86}

2.4.2 Bond order dependence

A bond like C-2/C-3 for compound **9-V** is called the intervening bond, figure 6. For four esters a correlation is established between $^2\Delta C(OD)$ and the bond order of the intervening bond.¹² For keto-enamines, coherence is shown between $^2\Delta C(ND)$ and the C-N bond order. The C-N bond order is found, form the barrier of the Z to E isomer rotation around the C-N bond.⁸¹ Increasing bond order results in larger two bond isotope effects and therefore increasing hydrogen bond strength. The correlations between the bond order and the hydrogen bond strength supports the idea that resonance assistance is a significant feature for this type of hydrogen bond.

2.4.3 Donors and acceptors

Based on two bond deuterium isotope effects on ^{13}C chemical shifts the following trends are found; the hydrogen bond strength decreases in the order $OH > SH > NHR$ for the donors, using esters as acceptors, and the hydrogen bond strength decreases in the order ketones > aldehydes > esters for the acceptors, using phenols as donors.⁷⁸

2.4.4 Isotope effects in tautomeric systems

In 1982 Hansen *et al.*⁸⁸ suggested deuterium isotope effects on ^{13}C chemical shifts as an useful method for the detection of fast tautomeric equilibria in an $A \rightleftharpoons B$ systems, in figure 2. This have been supported in several works.^{32,64,65,78}

Katritzky *et al.*³² showed by a correlation of $\log ^2\Delta C(XD)$ vs. $\delta(XD)$ for non-tautomeric compounds, that compounds which fall off the correlation possess tautomerism.

The two bond isotope effects observed for an asymmetric tautomeric system is very large^{64,65,88} whereas the four bond effects are smaller, and of both signs.^{64,65,88} In general, the isotope effects observed for asymmetric tautomeric systems are larger than in non-tautomeric systems, due to the contribution from the equilibrium isotope effect.⁸⁸

Bordner *et al.*⁶⁴ suggested that the isotope effect on the equilibrium vary as a function of the equilibrium constant that is the tautomeric equilibria have different susceptibility to changes due to deuteration, depending on the position of the tautomeric equilibrium. It has been shown, that the largest change in tautomeric equilibrium is observed for, $K = 0.3$ and $K = 3$ upon deuteration at OH. The change in the tautomeric equilibrium is zero at $K = 1$, and

approaches zero when K approaches zero or infinity.

Recent work showed that deuterium isotope effects on ^{13}C chemical shifts for proton transfer reactions in ortho mannich bases^{76,89} as a function K , was found to behave as predicted by Bordner *et al.*⁶⁴ Rospenk *et al.*^{76,89} in vague terms interpreted these results as a change in charged distribution.

In 1996, profound work dealing with deuterium isotope effects on ^{15}N chemical shifts for proton transfer reactions in acids - pyridine- ^{15}N complexes⁹⁰ was published. In this work, $^1\Delta^{15}\text{N}(\text{D})$ as a function $\delta^{15}\text{N}$, very nicely reproduced the course suggested by Bordner *et al.*⁶⁴ In an equilibrium system, $\delta^{15}\text{N}$ is a measure of the equilibrium constant. The experiments were carried out at low temperature (100 - 150K). In this temperature range, the slow proton- and hydrogen bond exchange, leads to resolved NMR lines for each hydrogen bonded species and their isotopomers. This means, that each complex is isolated, and that the intermolecular exchange is slow on the NMR time scale, but proton transfer from donor to acceptor within the complex is still fast. Smirnov *et al.*⁹⁰ interpreted these results as a gradual proton transfer to pyridine due to an increase of the acidity of the proton donor. In this work the acid-base equilibrium is disregarded. This interpretation is clearly not in accordance with the interpretation by Hansen *et al.*⁸⁸ and Bordner *et al.*⁶⁴

2.4.5 Isotope effects on fluorine chemical shifts

The large shift range and high sensitivity of ^{19}F makes this nuclear very suitable for NMR studies.

Isotope effects on ^{19}F chemical shifts have been thoroughly studied for non-hydrogen bonded systems.^{10,91,92} ^{19}F chemical shifts have been used with success to monitor tautomeric equilibria.^{93,94}

Rae *et al.*⁹⁵ measured a spin-spin coupling constant between the aromatic fluorine and the nitrogen and the carbon of the amide group in 2-fluorobenzamide and its N-methyl derivate. This coupling constant is absent in the corresponding N,N-dimethyl amide. The coupling is believed to be mediated via an intramolecular hydrogen bond, from the amid proton to fluorine.

3. Results

The number of the compound and atoms given here, are the same as in the included papers. The Roman number after the numbers of the compounds refers to the paper. E.g. **18-II** is compound **18** in paper II.

For each subject discussed, only a few data are shown. Further data and discussion of these are found in the papers in the appendix.

3.1 Localized hydrogen bond

3.1.1 Perturbations of equilibrium

An intramolecular hydrogen bond is weakened when hydrogen is substituted for deuterium,^{36,65,77} which is shown in a series of 2,6-dihydroxy acyl aromatic compounds. The acyl group in 2,6-dihydroxy acyl aromatic rotates fast at room temperature and average ^1H and ^{13}C spectra are observed (figure 7). When treating these compounds with a mixture of MeOH/MeOD, an isotopomeric mixture of double deuterated (DD), non-deuterated (HH) and mono-deuterated (HD/DH) result. The ^1H spectrum at room temperature of this isotopomeric mixture shows two OH signals, one from HH and one from HD/DH, the latter at the highest frequency. The ^1H chemical shifts of the hydrogen bonded OH is observed at higher frequency than the non-hydrogen bonded. The higher frequency of the observed average shift of HD/DH is due to a contribution of more than 50% from the hydrogen bond OH and less than 50% from the non-hydrogen bonded. Thence, form A in figure 7 are the preferred, in which the hydrogen bond constitute hydrogen not deuterium.

Δ_{SIP} (Splitting caused by Isotope Perturbation of equilibrium), is observed in the ^1H spectrum as the difference in the two OH signals, $\Delta_{\text{SIP}} = \delta\text{H}_{\text{HD/DH}} - \delta\text{H}_{\text{HH}}$. Δ_{SIP} is also observed for C-2/C-6 in the ^{13}C -spectrum (figure 7). From both ^1H and ^{13}C spectra the degree of perturbations can be determined. The degree of perturbations is determined from Δ_{SIP} and the chemical shifts observed in the fixed conformation at low temperature. The isotope effect has to be included for determination of the degree of perturbation using ^{13}C data. The perturbations for ketones are around 1.6 % and for esters 1.1%. The larger perturbation for ketones compared

with esters is ascribed to the stronger hydrogen bond in ketones.

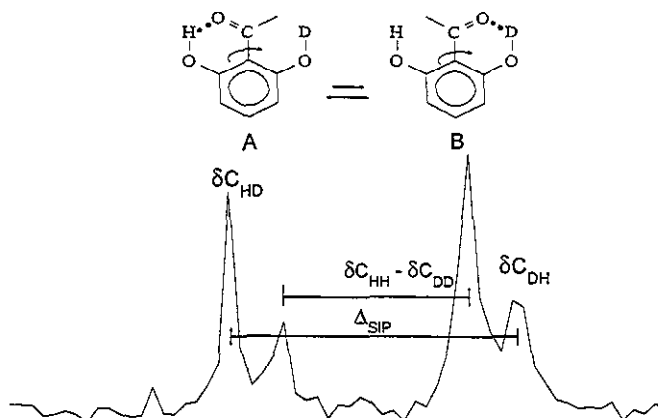


Figure 7. Monodeuterated isotopomers and the ^{13}C NMR spectrum of C-2, C-6 illustrating the Δ_{SIP} splitting and the intrinsic, average isotope effect, $\delta\text{C}_{\text{HH}} - \delta\text{C}_{\text{DD}}$ (Paper I)

For 2-hydroxy-6-methoxy-3-nitroacetophenone (7-IX) (figure 8), unusual isotope effects, compared with 2-hydroxyacetophenone, are observed. The isotope effects observed for 7-IX are much larger than expected for a substituted 2-hydroxyacetophenone and they are observed throughout the system. These isotope effects arise from a perturbation of the equilibrium, $\text{A} \rightleftharpoons \text{B}$ figure 8. The different in the ^{13}C chemical shifts for form A and B will when the equilibrium is shifted average to different chemical shifts.

^1H and ^{13}C resonances are observed for both of the forms at 160K, whereas averaged signals are observed at 300K. The value of $\delta(\text{OH})$ suggests that, the hydrogen bond to the acetyl group is stronger than the hydrogen bond to the nitro group. This is conformed by comparing $\delta(\text{OH})$ and $^2\Delta(\text{OD})$ for 2-nitrophenol and 2-hydroxyacetophenone. At ambient temperature, the B form (figure 8) dominates, as seen from the average $\delta(\text{OH})$ at higher temperatures compared with the separate $\delta(\text{OH})$ of the two forms observed at 160K. The amount of form B decreases with decreasing temperature. The finding that the at room temperature dominating form, becomes less abounded at low temperature, is unusual. This can be explained by assuming that ΔS for the B form is positive and large enough to overcome the difference in ΔH between the two forms. The difference in ΔH is due to a much weaker intramolecular

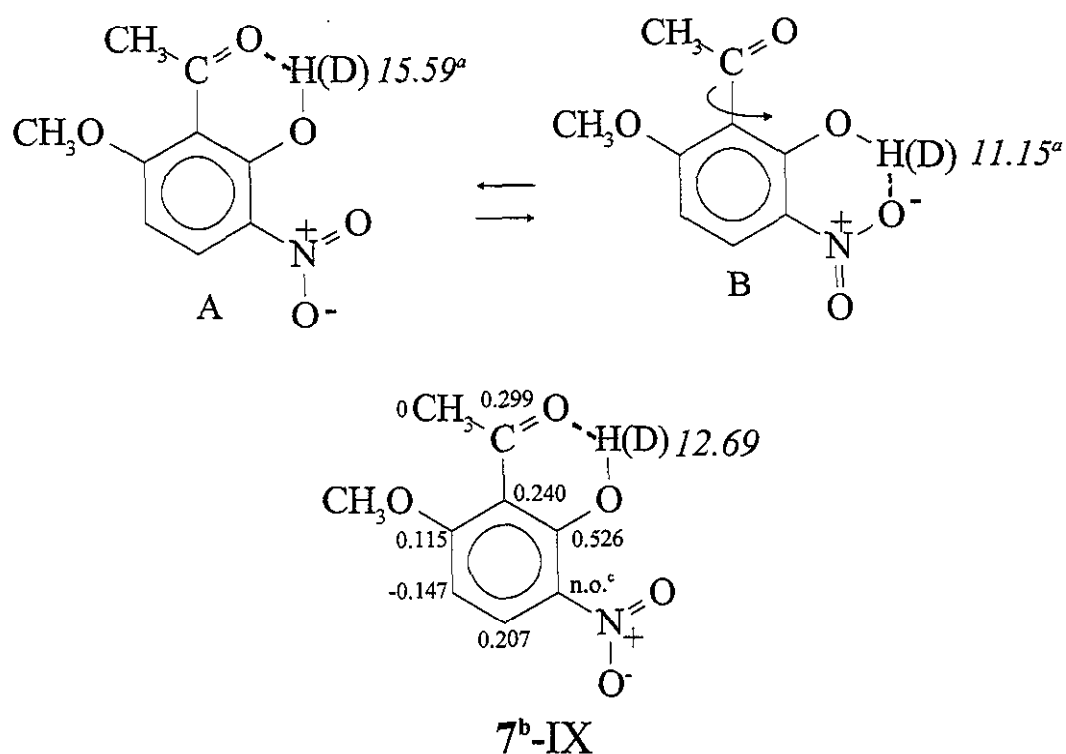


Figure 8. Deuterium isotope effects on ¹³C chemical shifts and $\delta(\text{OH})$ (italic) in ppm. The two rotamers of 7-IX, (A and B). a: 160K, b: 300K, c: Not observed. (Paper IX)

hydrogen bond to the nitro group in form B, compared to the hydrogen bond to the acetyl group in form A. The nitro group in form A is most likely subject to hindered rotation due to conjugation, whereas the acetyl group in form B rotate more freely, which can accounts for the more positive ΔS for the B form.

3.1.2 Steric hindrance

Weakening of intramolecular hydrogen bonds by introducing deuterium, can be used to reveal sterical hindrance. A weaker hydrogen bond allows a relaxation of the sterical hindrance. The resulting conformational change causes changes in the chemical shifts. These are observed as larger or smaller isotope effects, depending on whether the effects add or subtract.

In figure 9, examples of a sterical hindered compound, 9-II, and a non-sterical hindered compound, 10-II are given. $^2\Delta(\text{OD})$ is larger for 9-II than for 10-II though $\delta(\text{OH})$ is higher for 10-II. It should also be noted that $^5\Delta\text{CH}_3(\text{OD})$ becomes less negative in 9-II.

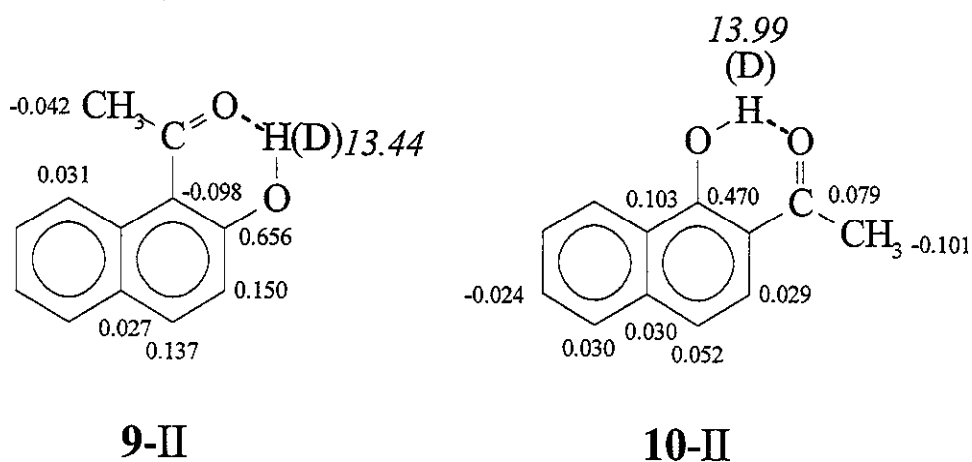


Figure 9. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (*italic*) in ppm, at 300K in CDCl_3 , for compound **9-II** and **10-II**.¹²

The two bond deuterium isotope effects on chemical shifts are shown to be good indicators for steric hindrance when plotted as a function of $\delta(\text{OH})$, figure 10.

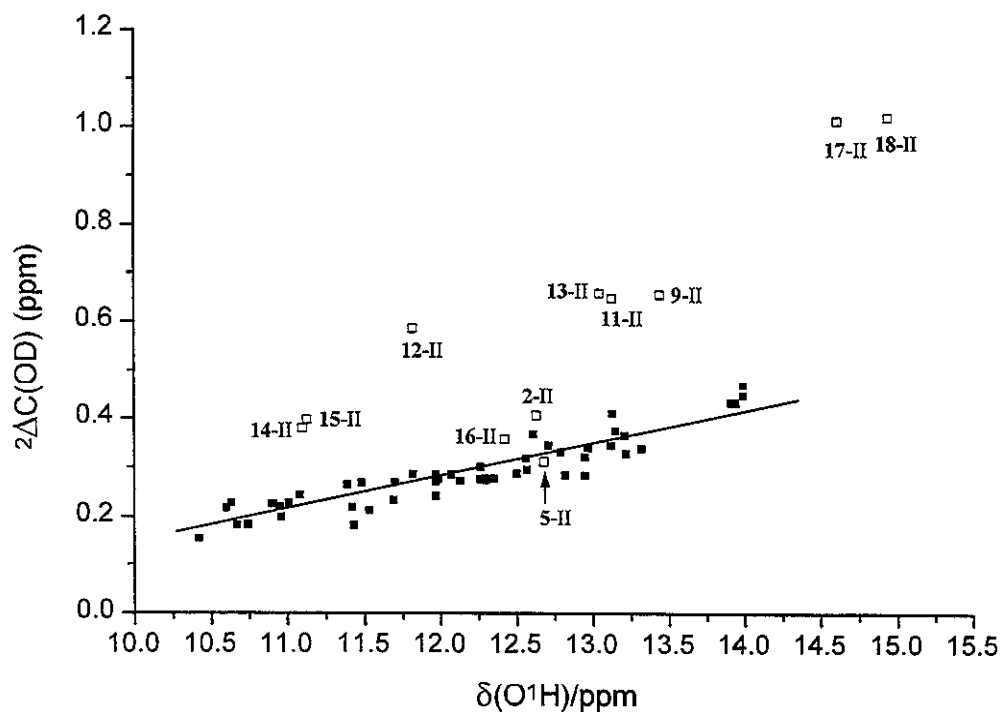


Figure 10. $2\Delta\text{C}(\text{OD})$ vs. $\delta(\text{OH})$, for a series of sterical hindered *o*-hydroxy acyl aromatics, \square , and non-sterical hindered *o*-hydroxy acyl aromatics, \blacksquare , ref. 12. (Paper II).

The data for compounds that are sterical hindered are above the correlation line for *o*-hydroxy acyl aromatics. 2-hydroxy-4,6-dimethylacetophenone, **2-II**, 2-hydroxypivalophenone, **5-II**, and 3-acetyl-4-hydroxypyrene, **16-II**, is expected to be steric hindered but this cannot be seen from the two bond deuterium isotope effects, as seen in figure 10.

The C-D bond is shorter than the C-H bond.^{60,61} When deuterium is introduced in the methyl group of **18-II** (figure 11) the average size of the methyl group decrease, allowing the acetyl group to come into the aromatic plane. Hereby the hydrogen bond strength and the $\delta(\text{OH})$ are increased (Figure 11). The $\delta(\text{OH})$ for the fully deuterated acetyl group ($x = 3$ in figure 11) is observed at high frequency and for the non-deuterated acetyl group ($x = 0$ in figure 11) at the low frequency.

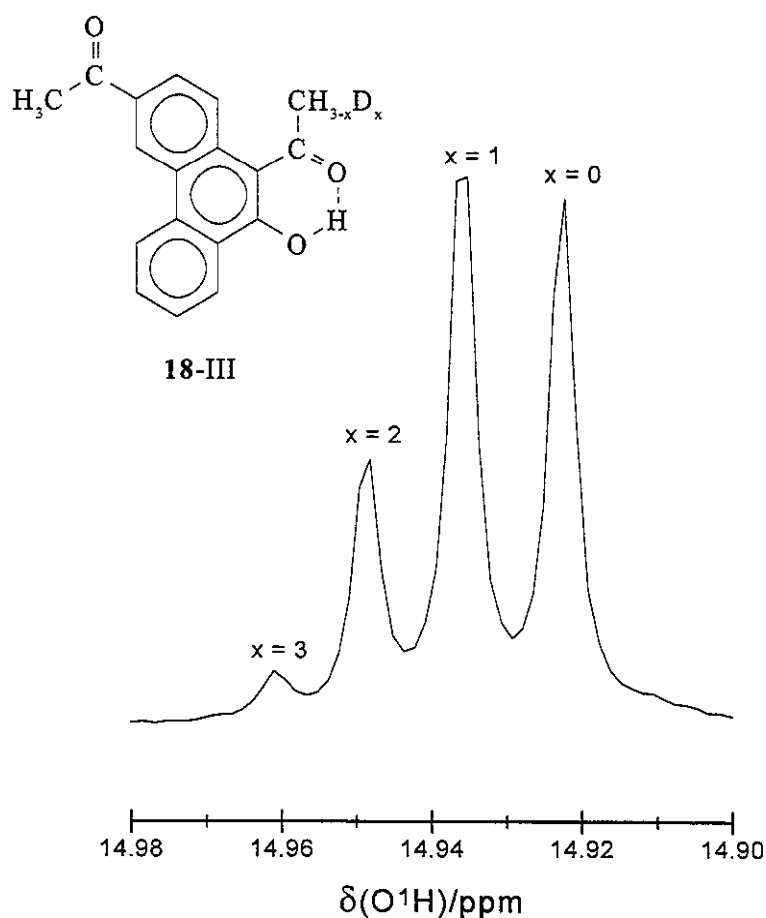


Figure 11. The OH region of the ^1H spectrum for **18-II**, deuterated at the methyl group. $x = 3$ fully deuterated acetyl group and $x = 0$ non-deuterated acetyl group. (Paper II).

Steric hindrance can also be verified by carbon-fluorine coupling constant, $J(\text{F},\text{C})$. This is shown for 2-hydroxy-6-fluoropivalophenon, **6-II**. Figure 12.

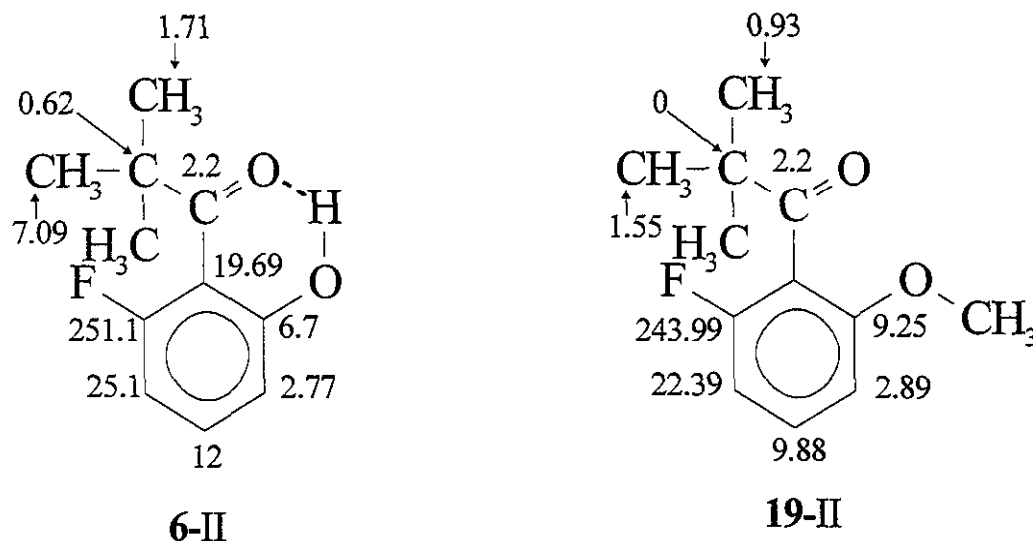


Figure 12. Carbon-fluorine and proton-fluorine couplings constant in Hz. (Paper II).

A through space $J(\text{F},\text{CH}_3)$ of 7.09 Hz was found for **6-II** compared with 1.55 Hz for **19-II** showing that the pivalo group is twisted further out of the aromatic plane in the non-hydrogen bonded compound, **19-II**. On lowering the temperature from 300K to 215K the, $J(\text{F},\text{CH}_3)$ increases from 7.09 Hz to 7.57 Hz for **6-II**, in agreement with a shorter F - CH_3 distance. This is consistent with the increase in $\delta(\text{OH})$ on lowering the temperature, suggesting a stronger hydrogen bond. Upon deuteration at OH, the $J(\text{F},\text{CH}_3)$ decreases to 6.92 Hz (figure 12). This value is the upper limit as only 30% deuteration was achieved, and separate resonances from the H and D isotopomers could not be obtained. This decrease reflects the steric hindrance, given when the pivalo group is twisted further out of the aromatic plane, due to weakening of the hydrogen bond upon deuteration.^{36,96}

Steric hindrance for N-phenyl keto-enamines is also observed as a decrease in $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{ND})$, for **19-VII** compared with **15-VII**, figure 13. The 2,6-dimethyl N-phenyl group is twisted due to steric interaction with the C-1 methyl group. The twist of the N-phenyl group decreases the positive charge on N, due to decreasing conjugation to the N-phenyl group. This leads to a weaker hydrogen bond observed as lower $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{ND})$ values.

$^2\Delta\text{C}(\text{ND})$ is underlined in figure 13.

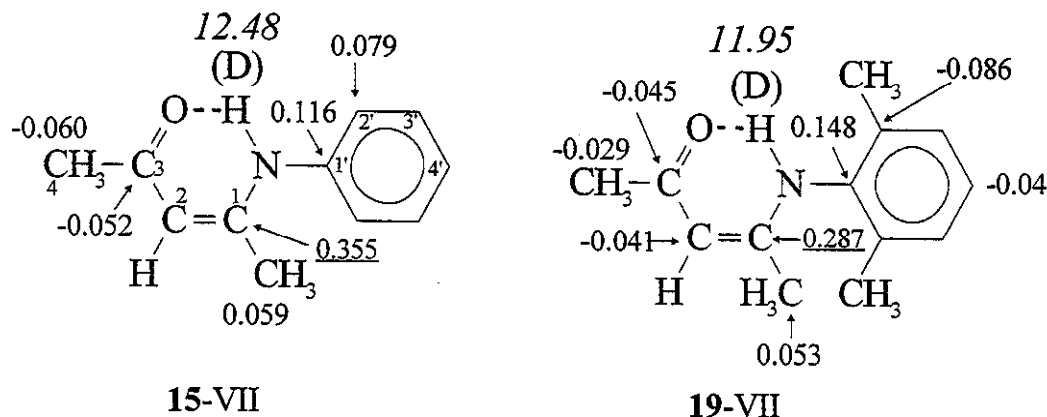


Figure 13. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{NH})$ (italic) in ppm, at 300K in CDCl_3 . $^2\Delta\text{C}(\text{ND})$ is underlined. (Paper VII).

The twist in the N-phenyl group out of the plane is also observed on the isotope effects on C-2' (figure 13). The isotope effect on C-2' is positive when the steric interaction is small and the N-phenyl group is expected to be nearly planar. The isotope effect on C-2' is negative when the steric interaction becomes very pronounced as observed for 19-VII. The C-1 methyl substituted keto-enamines and C-1 non-substituted keto-enamines fall on two different lines in a plot of $^3\Delta\text{C}-2'(\text{ND})$ vs. $^2\Delta\text{C}-1(\text{ND})$, figure 14.

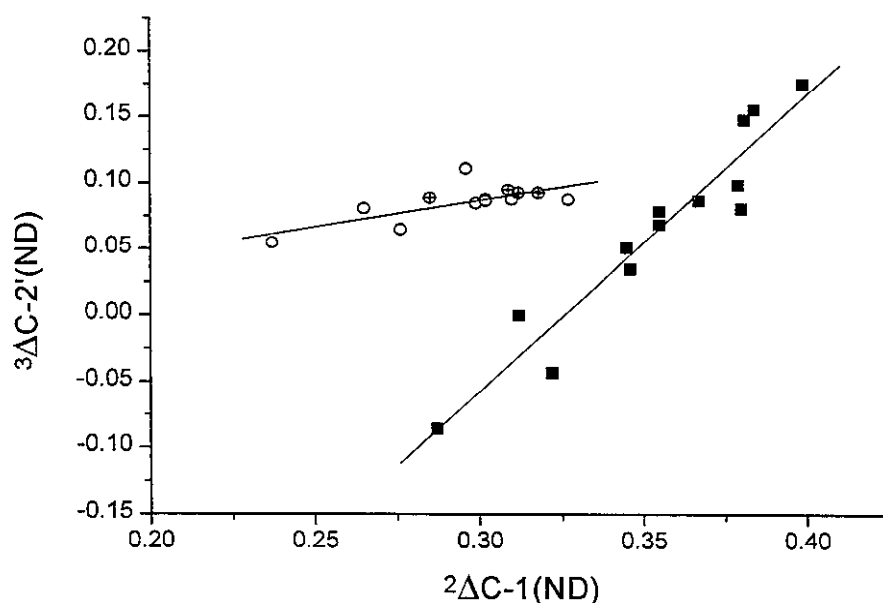


Figure 14. $^3\Delta\text{C}-2'(\text{ND})$ vs. $^2\Delta\text{C}-1(\text{ND})$ for N-phenyl keto-enamines. C-1 methyl substituted, ■, C-1 unsubstituted, ○, and C-1 unsubstituted from ref. 81, ⊕. (Paper VII).

An electron donating group in the *p*-position of the N-phenyl group results in a decrease of $^2\Delta C-1(ND)$ and $^3\Delta C-2'(ND)$, due to a more pronounced twist, when the N-C-1' double bond character decreases. The opposite is observed for an electron withdrawing group in the N-phenyl *p*-position.

3.1.3 Steric compression

Another type of steric interaction is observed when an angle or bond is compressed instead of twisted. This steric interaction is called steric compression.

For C-1 methyl substituted N-phenyl keto-enamines, where the steric interaction is less pronounced than in the case of twisted, is steric compression found. There is a fine balance between a planar structure which optimize the hydrogen bond strength, and a twist of the N-phenyl group, to reduce the sterical strain. In this fine balance a compression of the O---N distance is observed. This is seen when $^2\Delta C-1(ND)$ and $\delta(NH)$ is compared for **1Z-VII** and **10Z-VII**, figure 15. The C-1 methyl group on **10Z-VII** compresses the O---N distance compared with **1Z-VII**, observed as an increase in $\delta(NH)$ and $^2\Delta C(ND)$ for **10Z-VII**.

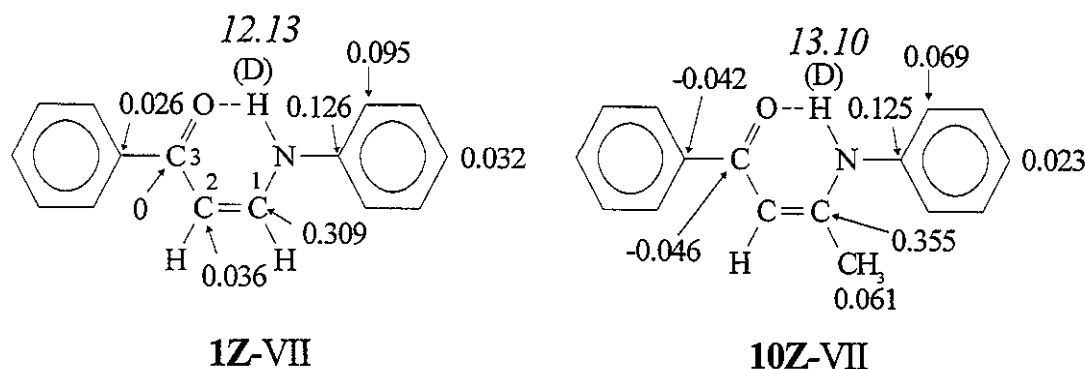


Figure 15. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(NH)$ (italic) in ppm, at 300K in $CDCl_3$. (Paper VII).

Further sterical interaction results in a twist for the N-phenyl group out of plane as seen for **19-VII**, figure 13. For the N-phenyl keto-enamines compression causes a positive contribution to $^2\Delta C-1(ND)$ and the twist causes a negative contribution.

In the 2-acyl-1,3-indandione system, $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{OD})$ are seen to display a steady increase when the size of the acyl group increases from acetyl (**35-III**), propionyl (**36-III**) to iso-butyryl (**37-III**). A dramatic increase in $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{OD})$ is observed for pivaloyl (**38-III**) (Figure 16).

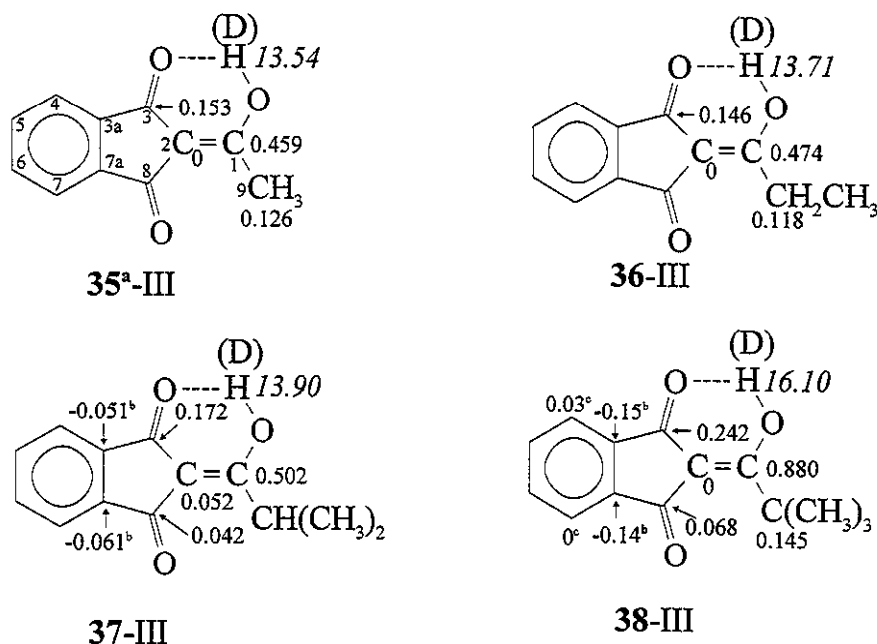


Figure 16. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (italic) in ppm at 190K, in CD_2Cl_2 . a: Temperature 180K. b and c: Maybe interchange, assignment tentative. (Paper III).

From the increase of $\delta(\text{OH})$ steric hindrance can be ruled out, as steric hindrance is known to give a decrease in $\delta(\text{OH})$ due to the less favourable hydrogen binding geometry. The large $^2\Delta\text{C}(\text{OD})$ and $\delta(\text{OH})$ found for **38-III** is explained by steric compression that decreases the O--O distance, resulting in an increase in hydrogen bond strength.

The ^{13}C chemical shifts of **35-III** - **39-III** shows only small variations with temperature, which suggests that these compounds are non-tautomeric and exclusively on the form shown in figure 16.

In a plot of $\delta(\text{OH})$ vs. $^2\Delta\text{C}(\text{OD})$ (figure 17) the data for **35-III** to **39-III** are seen to be on the correlations line with the non-tautomeric five-membered ring β -diketones, suggesting that these compounds are non-tautomeric as well.

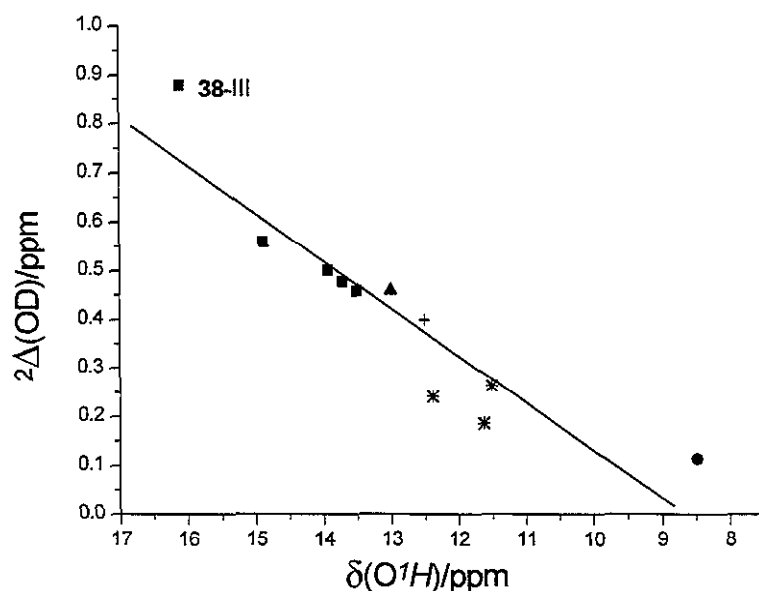


Figure 17. ${}^2\Delta C(OD)$ vs. $\delta(OH)$ for five-membered ring ketones. *, data from ref. 97, ● 1-hydroxy-9-florenone,⁷⁵ ▲, data from ref. 62, +, 18-V and ■ is compound 35-III to 39-III. (Paper III).

3.1.4 Two donors, one acceptor

1,5-diphenyl-pentane-1,3,5-trione can exist in two enolic forms, a symmetric form, 3-IV and a non-symmetric form, 4-IV (figure 18). The ratios of the two forms depend on the solvent. In CD_2Cl_2 only the symmetric form is present. The effect of two donors to one acceptor can be tested from the compounds 3-IV and 4-IV. The same is seen for 2-IV compared with 1-IV, figure 26. A large negative isotope effect of -0.140 ppm is observed on OH-5 for 3-IV when OH-1 is deuterated. This increase in the $\delta(OH)$ for OH-5 upon deuterium substitution on OH-1 indicates a stronger hydrogen bond for OH-5. Deuteration at OH-1 weakens this hydrogen bond, which increase the OH-5 hydrogen bond strength as the two donors compete for one acceptor.

The non-tautomeric systems 5Z-VII, 6Z-VII, 9-IX and 22¹² (figure 18) are excellent for testing the effect of two donors to one acceptor. 5Z-VII and 9-IX both have lower $\delta(OH)$ and ${}^2\Delta C(OD)$ values compared with 6Z-VII and 22,¹² respectively. This reflects a weakening of the hydrogen bond when two donors compete for one acceptor.

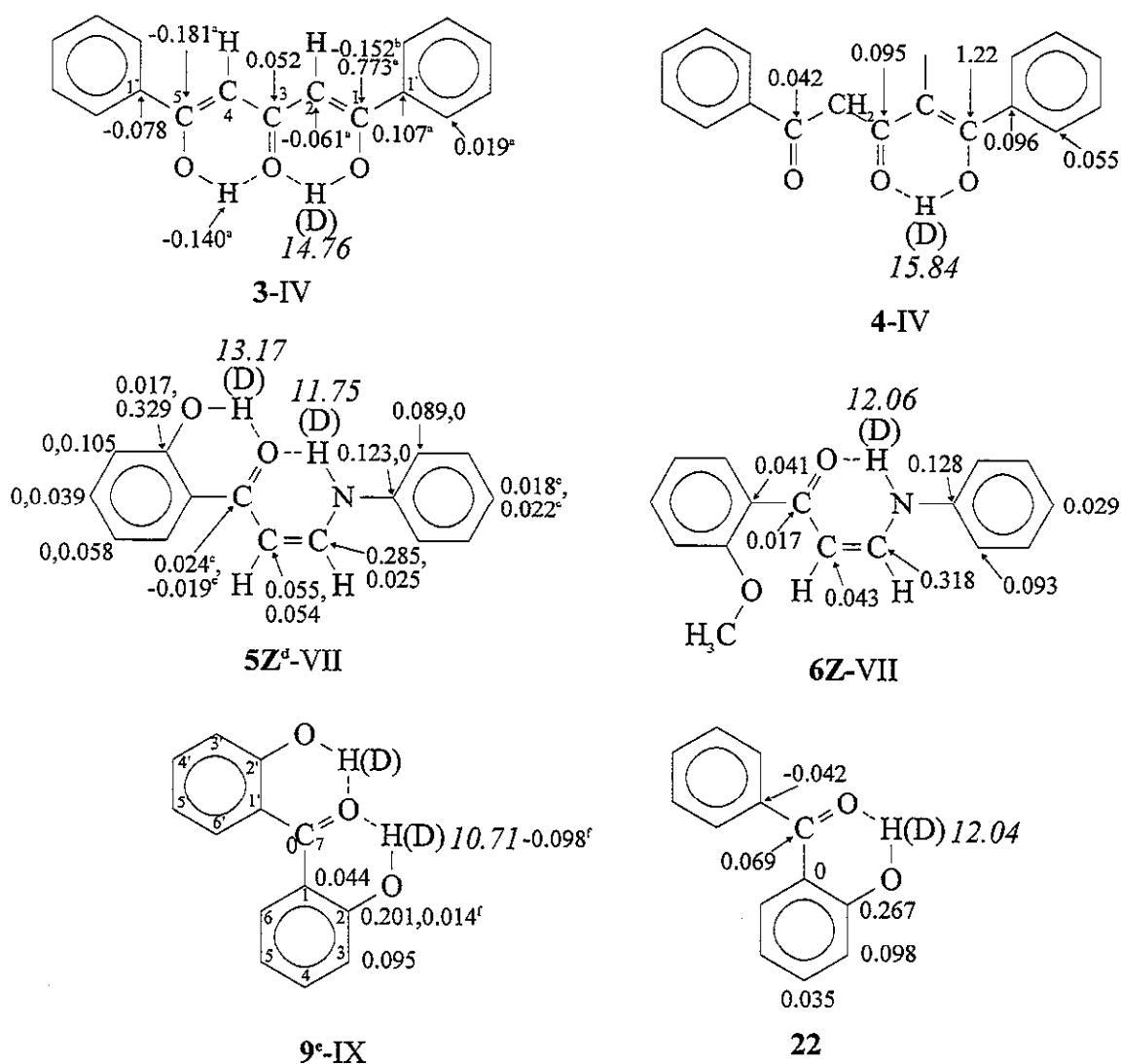


Figure 18. Deuterium isotope effects on ^1H and ^{13}C chemical shifts, $\delta(\text{NH})$ and $\delta(\text{OH})$ (*italic*) in ppm at 300K in CDCl_3 . Data for **22** are from ref. 12. *a*: Due to deuterium at OH-1, *b*: Due to deuterium at OH-5, *c*: Maybe interchange, *d*: Deuterium isotope effects are given in the order $^{\text{a}}\Delta\text{C}(\text{ND})$, $^{\text{a}}\Delta\text{C}(\text{OD})$, *e*: 260K, *f*: Due to deuterium at OH-2'. (Paper IV, VII and IX).

The substituent effect of a hydroxy group at C-2' for **9-IX** is expected to increase the hydrogen bond strength,¹² however a decrease is observed due to two donors competing for one acceptor, judge from the $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{OD})$. The large negative isotope effect on OH observed for **9-IX**, supports that two donors competing for one acceptor cause a weakening the hydrogen bond. Exchanging hydrogen with deuterium in one hydrogen bond, weakens this hydrogen bond and thereby strengthen the other hydrogen bond. A stronger hydrogen

bond is observed as a higher OH resonance frequency, and cause a negative isotope effect. The Z form of **5-VII**, **5Z-VII**, can also be compared with **5E-VII**, which is the E form of **5-VII**. **5E-VII** only form one hydrogen bond. The values of $\delta(\text{OH})$ and $^2\Delta\text{C}(\text{OD})$ for **5E-VII** suggest a stronger hydrogen bond than for **5Z-VII**, which also shows that two donors competing for one acceptor result in weakening of the hydrogen bond.

3.2 Deuterium isotope effects in tautomeric systems

Enolic β -diketones are known to exist as two fast interchanging tautomers. The tautomeric equilibrium can be changed by varying the solvent or the temperature, the ^{13}C chemical shifts display a linear change as a function of temperature (figure 19). $\delta^{13}\text{C}$ -3 increase and $\delta^{13}\text{C}$ -1 decrease with decreasing temperature showing that the equilibrium is displaced in favour of form A at lower temperature (figure 19). Large deuterium isotope effects are observed for enolic β -diketones, due to contributions from the equilibrium isotope effect. The equilibrium isotope effect arises from change in the equilibrium upon exchanging hydrogen for deuterium. Due to the contribution from the equilibrium isotope effects in the observed isotope effects, large isotope effects are observed throughout the system for tautomeric compounds. These isotope effects can be both positive or negative.

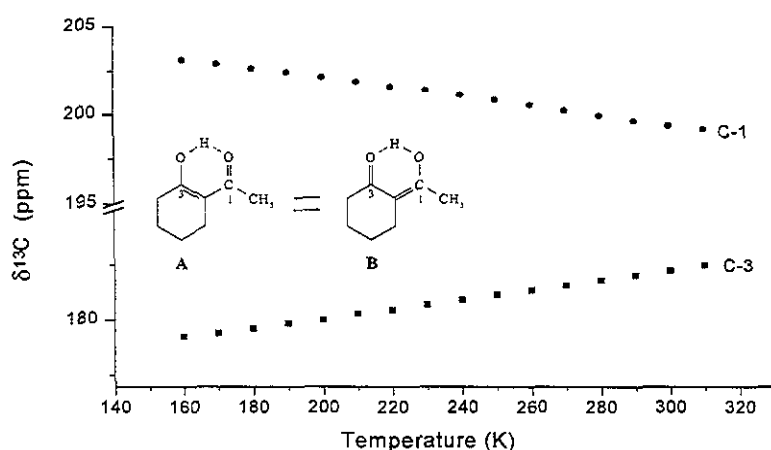


Figure 19. $\delta^{13}\text{C}$ -1 and $\delta^{13}\text{C}$ -3 for **9-V** as a function of temperature. The tautomerism of **9-V**. (Paper V).

Deuterium isotope effects for enolic β -diketones also display temperature dependence, as shown for C-1 and C-3 for 9-V in figure 20. A largest temperature dependence is seen for $\Delta C-1(OD)$ and $\Delta C-3(OD)$, but all the observed isotope effects display temperature dependence.

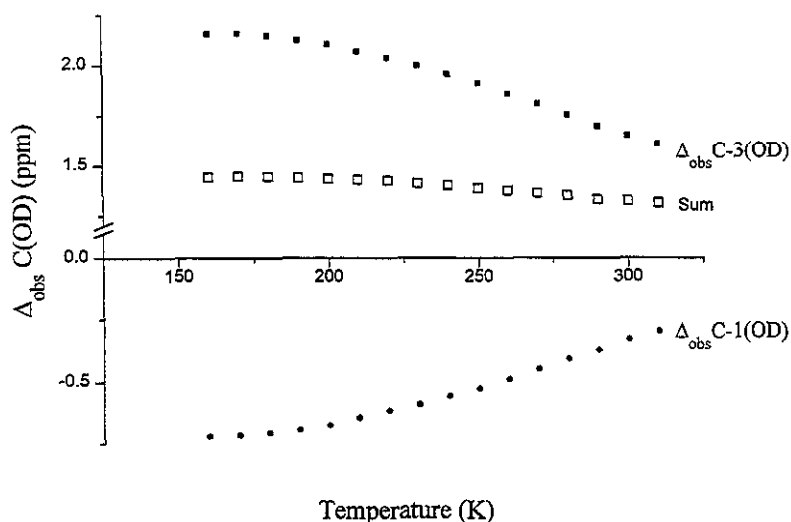


Figure 20. Deuterium isotope effects on $^{13}\text{C}-1$ and $^{13}\text{C}-3$ chemical shifts for 9-V and the sum of these as a function of temperature. (Paper V).

The numeric increase in the isotope effects and levelling of these at lower temperatures, suggests that the change in equilibrium due to deuterations, ΔX_D , depends upon the mole fraction, X , as suggested by Bordner *et al.*⁶⁴

When $\Delta C-1(OD)$ and $\Delta C-3(OD)$ are summed up, the equilibrium contributions are cancelled. This sum is seen to be nearly temperature independent as expected for intrinsic isotope effects. The sum of $\Delta C-1(OD)$ and $\Delta C-3(OD)$ is equal to the sum of ${}^2\Delta_{\text{int}}C(OD)$ and ${}^4\Delta_{\text{int}}C(OD)$.

A sum above 0.8 ppm for five-membered rings and 1.2 ppm for six-membered rings and open enolic β -diketones, is observed for compounds with a mole fraction different from zero or 1. This makes the sum a helpful tool to determine whether the compound is tautomeric or not. This rule of thumb for enolic β -diketones has with some success been applied to other systems.

3.2.1 Tautomeric equilibrium constants

To get a more quantitative description of how ΔX_D depends on X, X has to be determined.

Geraldes *et al.*⁹⁸ proposed a method, based on estimated ^{13}C chemical shifts, (eq. 9) for enolic β -diketones, using structurally related enolic β -keto esters (figure 21). $\delta_{\text{obs}}^{13}\text{C}$ is the observed carbonylic or enolic chemical shift of the enolic β -diketone in question.

$$K = (1-X)/X = (\delta^{13}\text{C}=\text{O} - \delta_{\text{obs}}^{13}\text{C})/(\delta_{\text{obs}}^{13}\text{C} - \delta^{13}\text{C}-\text{OH}) \quad (\text{eq. 9})$$

The ^{13}C chemical shifts of the enolic carbon for enolic β -keto ester, ($\delta^{13}\text{C}-\text{OH}$) is used as the ^{13}C chemical shifts of the enolic β -position, see compound **31-V**, figure 21. Using $\delta^{13}\text{C}-\text{OH}$ from the enolic β -keto ester the carbonyl ^{13}C chemical shifts ($\delta^{13}\text{C}=\text{O}$) can be derived from the observed averaged ^{13}C chemical shift of the symmetric enolic β -diketones ($\delta^{13}\text{C}_{\text{sym}}$) as shown in eq. 10.

$$\delta^{13}\text{C}=\text{O} = 2\delta^{13}\text{C}_{\text{sym}} - \delta^{13}\text{C}-\text{OH} \quad (\text{eq. 10})$$

The symmetric enolic β -diketone and the enolic β -keto esters are structurally related like enolic acetylacetone and ethyl acetoacetate (figure 21), which includes the substituent effect in the estimated ^{13}C chemical shift.

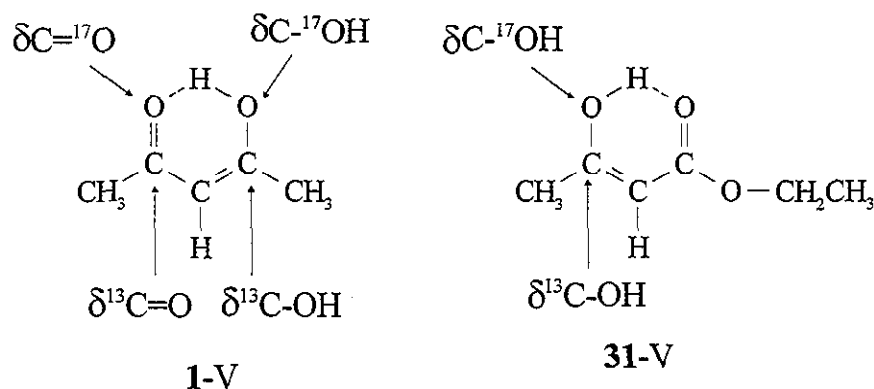


Figure 21. Chemical shifts from enolic β -keto ester used as model chemical shifts to find the separate chemical shifts for enolic β -diketones.

The same principle is also used to estimate the ^{17}O chemical shifts. The molar fractions are also estimated from ^{17}O chemical shifts using the method proposed by Geraldes *et al.*⁹⁸ (eq. 9) and the method proposed by Gorodetsky *et al.*⁹⁹ (eq. 11). The method of Gorodetsky *et al.*⁹⁹ uses the estimated ^{17}O chemical shift difference between the enolic and carbonylic ^{17}O chemical shift, ($\delta\text{C}=\text{}^{17}\text{O} - \delta\text{C}-\text{}^{17}\text{OH}$), Δ , and the observed chemical shift difference between

oxygen 1 and 3, ($\delta^{17}\text{O}-1 - \delta^{17}\text{O}-3$), δ , (figure 21). The ^{17}O chemical shifts are estimated as described for ^{13}C chemical shifts, using the ^{17}O chemical shifts from enolic β -keto esters and symmetric enolic β -diketones.

$$K = (1-X)/X = (\Delta-\delta)/(\Delta+\delta) \quad (\text{eq. 11})$$

These three methods give nearly the same results for the open nearly symmetric enolic β -diketones. For the ring enolic β -diketones a difference of up to 0.11 in molar fractions is found by using the three different methods. The molar fraction determined by the methods of Gerald *et al.*⁹⁸ using ^{17}O chemical shifts are between the molar fraction determined by the methods of Gerald *et al.*⁹⁸ using ^{13}C chemical shifts and the methods of Gorodetsky *et al.*⁹⁹ using ^{17}O chemical shifts.

3.2.2. Observed deuterium isotope effects on ^{13}C chemical shifts vs. the molar fraction

$\Delta\text{C}-1(\text{OD})$ and $\Delta\text{C}-3(\text{OD})$ measured for different enolic β -diketones display large variations as a function of the molar fraction, X . This variation is due to the tautomeric equilibria have different susceptibility to deuteration depending on the position of the tautomeric equilibrium, thence ΔX_D has different magnitudes for different X 's.

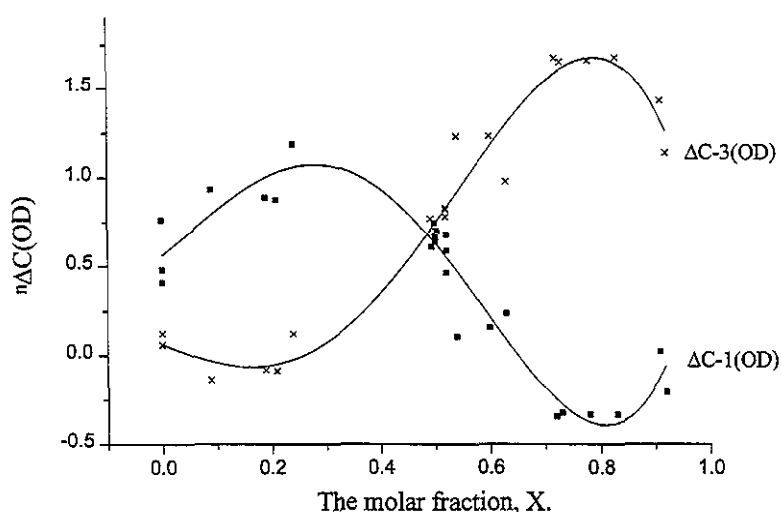


Figure 22. Observed deuterium isotope effects on C-3, \times , and C-1, \blacksquare , chemical shift in ppm as a function of the mole fraction X , for 24 enolic β -diketones. The curves are fitted for a fourth-order polynomial. (Paper V).

Smaller numeric values of the deuterium isotope effects are found for $X < 0.5$ than for $X > 0.5$. The data points for $X < 0.5$ are from five-membered ring systems, and the data points observed for $X \geq 0.5$ are from six-membered ring- and open enolic β -diketone systems. Five-membered ring systems form the weakest hydrogen bonds, resulting in smaller isotope effects. The data in figure 22 show some scatter due to the difference in the compounds and the error on the estimations of the molar fraction. To obtain a perfect curve in the plot of the isotope effects as a function of the mole fraction, the tautomeric equilibrium for one compound should be changed from $X \sim 0$ to $X \sim 1$ by changing the temperature. The largest change in X is obtained for enolic 2-acetylcyclohexanone **9-V**, $X = 0.75$ at 310K to $X = 0.87$ at 160K.

The deuterium isotope effects on ^{13}C chemical shifts and the mole fraction is determined for eight different enolic β -diketones at different temperatures. When these are plotted with the data in figure 22, the picture is more complex as shown in figure 23.

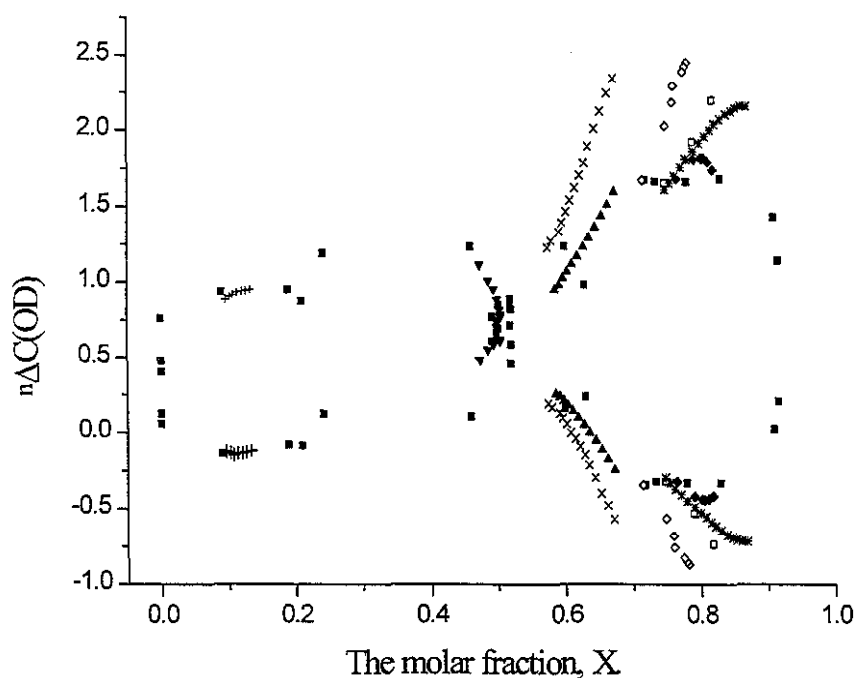


Figure 23. Observed deuterium isotope effects on C-3 and C-1 chemical shifts in ppm as a function of the mole fraction, X . ■, data shown in figure 22. Isotope effects and X at different temperatures for, **10-V**, □: **14-V**, ▲: **2-V**, ▼: **20-V**, ×: **15-V**, +: **12-V**, ◇: **11-V**, ◆ and **9-V**, *.

The deuterium isotope effects on ^{13}C chemical shifts as a function of X displays different curves for each compound, but the overall pattern is the same. The different curves for each compound reflect the difference in structure. The isotope effects for enolic 2-propionyl-cyclohexanone, 11-V, is seen to decrease when X increases above 0.8. For enolic 2-acetyl-cyclohexanone, 9-V, the increase in isotope effects is seen to level off when X increases above 0.8. In the region $X = 0 - 0.5$ the data points arises from the five-membered ring systems. Due to intermolecular exchange these systems need cooling to enable observations of the isotope effects and most of them are only observed at one temperature.

3.2.3 Change in the molar fraction due to deuteration vs. the molar fraction

ΔX_D can be estimated from eq. 8 where $\delta\text{C}^*=\text{O}(\text{H})$ and $\delta\text{C}^*-\text{OH}$ are estimated and $(X \times {}^2\Delta\text{C}^*-\text{OD} + (1-X) \times {}^4\Delta\text{C}^*=\text{O}(\text{D}))$ is approximately equal to a X fraction of the sum $(\Delta\text{C}-1(\text{OD})_{\text{obs}} + \Delta\text{C}-3(\text{OD})_{\text{obs}})$ in which the equilibrium dependence is cancelled. The plot of ΔX_D vs. X (figure 24) shows that ΔX_D goes through a minimum at $X \sim 0.2$ and a maximum at $X \sim 0.75$ in accordance with Bordner *et al.*⁶⁴ ΔX_D is zero for $X = 0.5$ and approach zero for X approaching zero or one.

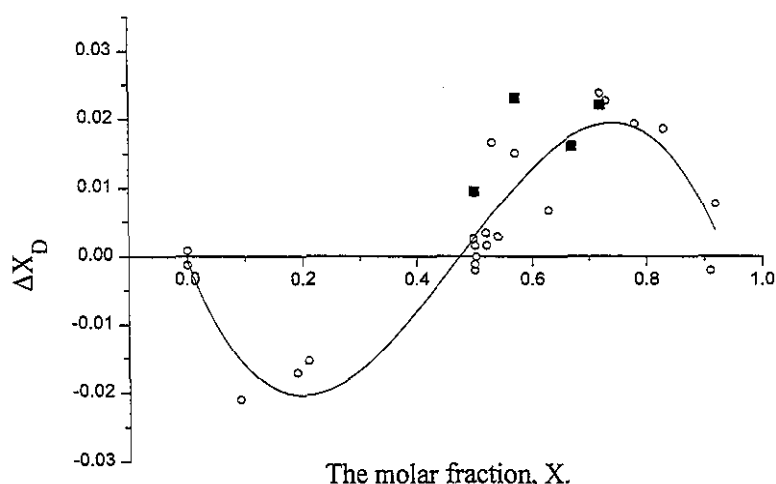


Figure 24. Change in the tautomeric equilibrium due to deuteration on OH, ΔX_D , as a function of the mole fraction, X . ○ is enolic β -diketones (Paper V), and ■ is 22 - 25 - VIII displaying azo/hydrazo tautomerism (Paper VIII).

This shows that the tautomeric equilibrium has different susceptibility to changes, due to deuteration, depending on the position of the tautomeric equilibrium. The azo/hydrazo tautomerism (figure 34) does not contradict this description of ΔX_D variations as a function of X , (figure 24).

3.3 Tautomeric or non-tautomeric

3.3.1 Two bond deuterium isotope effects vs. four bond deuterium isotope effects

In a plot of $^2\Delta C(OD)$ vs. $^4\Delta C(OD)$ the tautomeric open and six-membered rings enolic β -diketones show a correlation (figure 25). The non-tautomeric compounds are confined in a small region in this plot (figure 25). In the plot of $^2\Delta C(OD)$ vs. $^4\Delta C(OD)$ the tautomeric compounds are observed in a different region then the non-tautomeric. Therefore a plot of $^2\Delta C(OD)$ vs. $^4\Delta C(OD)$ can be used to point out tautomeric systems from non-tautomeric.

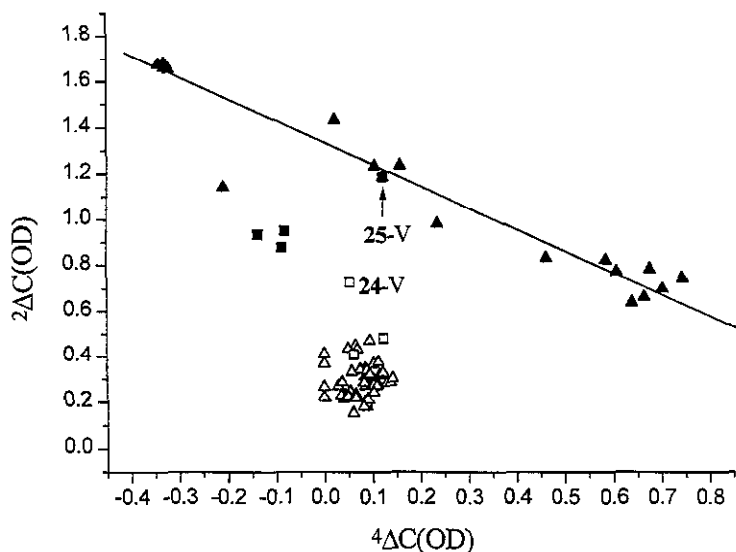


Figure 25. $^2\Delta C(OD)$ vs. $^4\Delta C(OD)$. Δ , non-tautomeric system from ref. 12, \blacktriangle tautomeric open and six-membered ring enolic β -diketones (Paper V), \blacksquare tautomeric five-membered ring enolic β -diketones, \square , non-tautomeric enolic β -diketones. (Paper V). $^2\Delta C(OD)$ and $^4\Delta C(OD)$ are defined as: $\Delta_{obs}C-3(OD) \sim ^2\Delta C(OD)$ for $X > 0.5$, $\Delta_{obs}C-1(OD) \sim ^2\Delta C(OD)$ for $X < 0.5$, $\Delta_{obs}C-3(OD) \sim ^4\Delta C(OD)$ for $X < 0.5$, $\Delta_{obs}C-1(OD) \sim ^4\Delta C(OD)$ for $X > 0.5$. For $X = 0.5$ is $^2\Delta C(OD) = ^4\Delta C(OD)$.

Compound **24-V** and **25-V** both have a sulfur atom in the five-membered ring. The sulfur atom expands the five-membered ring which make these two compounds an intermediate stage between five- and six-membered ring systems. Compound **24-V** is believed to be non-tautomeric but this is uncertain as can be seen from figure 25.

3.3.2 3,5-diacetyltetrahydropyran-2,4,6-trione

The ^1H and ^{13}C spectra of 3,5-diacetyltetrahydropyran-2,4,6-trione show two species **1-IV** and **2-IV** in CDCl_3 .²⁷ A major species **1-IV** and a minor that is symmetric (figure 26). The minor was suggested to be **2d-IV**.²⁷

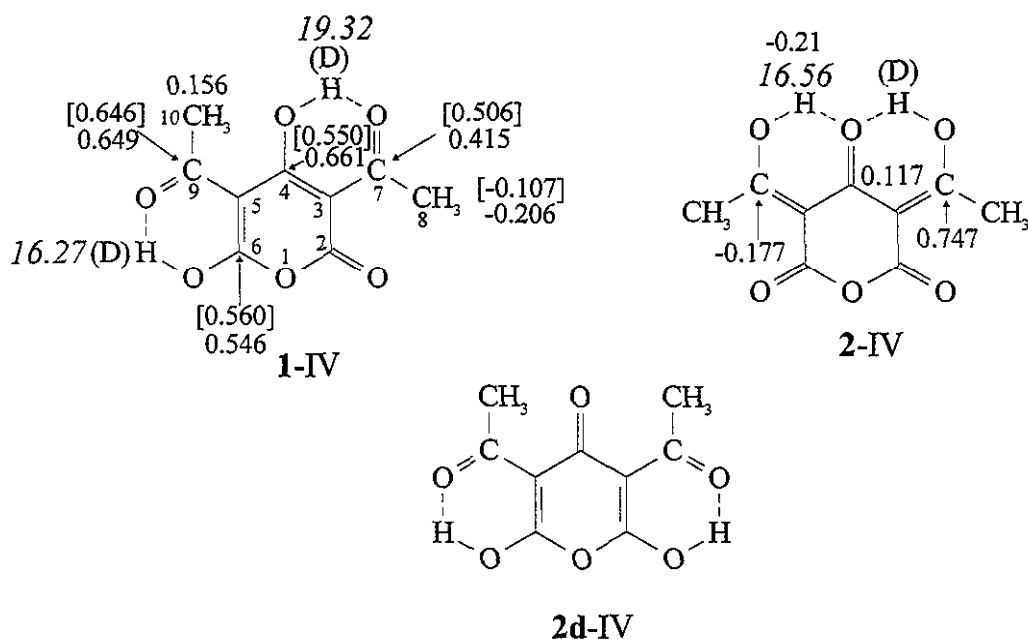


Figure 26. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (italic) in ppm, at 250K in CDCl_3 , values in square brackets were measured at 300K. (Paper IV).

Upon deuteration, the OH resonance for the minor species, splits into two with a splitting of 0.21 ppm at 250 K in CDCl_3 . This large negative isotope effect on the OH resonance is similar to those observed for **3-IV** and **9-IX** (figure 18) which shows that the minor form has two donors to one acceptor, indicating that the structure is **2-IV**. Furthermore, the C-7 and C-9 resonance splits into four resonances with the outer pair of resonances of equal intensity, in agreement with a large two bond isotope effect from OD-7, and a small long range effect from OD-9. C-4 split in to two resonances although three resonances are expected one from

each isotopomer, HH, HD and DD. The four large isotope effects observed on C-4, C-7, C-6, C-9, and the methyl groups indicate that **1-IV** must be a double tautomeric system, in accordance with Tan *et al.*²⁷ The approximately equal value found for the isotope effects on C-6/C-9 and C-4/C-7 shows that these are averaged two and four bond isotope effects, with an equilibrium constant close to one. The temperature dependence of the isotope effects observed on C-4 and C-7 shows also that **1-IV** is tautomeric. A sum of 1.20 ppm and 1.06 ppm is found for the isotope effects observed on C-6/C-9 and C-4/C-7, respectively. For six-membered ring and open enolic β -diketones a sum above 1.2 is shown to indicate tautomerism. The C-4/C-7 moiety for **1-IV** is found tautomeric although the sum is lower than 1.2 ppm. The finding that the carbonyl carbon of the anhydride moiety, C-6, is part of a tautomeric system, is unusual. Enolic β -keto esters are known as non-tautomeric.^{98,99} The anhydride moiety can be regarded as an ester made up of O-1, C-2 and O-2, C-6 is then a carbonyl carbon with the ability to form an enolic carbon.

3.3.3 Enolic β -ketoamides

The sum of the $\Delta C-O(D)$ and $\Delta C=O(D)$ above 1.2 ppm shows that the enolic β -ketoamides are tautomeric. The temperature dependence of the isotope effects and the large effects observed throughout the system also strongly suggest a tautomeric system (figure 27). Especially for the α -acetyl enolic β -ketoamides as **3e-VI**, large isotope effects are observed on C-6, C-1' and C-4'. The large isotope effect on C-1 shows that the C-1 enolic form is the dominating, as shown in figure 27. The amid carbon has less tendency to form an enolic carbon than the carbonyl carbon.

The coupling constant between the hydrogen bonded hydrogen to the carbon can also be used as a measure of tautomerism. For symmetric enolic β -diketones as acetylacetone (**1-V**), the coupling constant observed on C-1 and C-3 is 3.4 Hz.¹⁰⁰ For **2e-VI** this coupling to C-1 is 4.5 Hz and 2.3 Hz to C-7,¹⁰⁰ which also suggests that the enolic β -ketoamides are tautomeric. For **6e-VI** the hydroxy hydrogen coupling constant to C-1 is 5.4 Hz and less than 1 Hz on C-3.¹⁰⁰ The lack of coupling to C-3 indicates that this system is non-tautomeric or that the equilibrium is shifted far in the direction of the C-1 enolic form. In summary, of the present data, **6e-VI** is believed to be tautomeric, with the equilibrium shifted far in the direction of the C-1 enolic form.

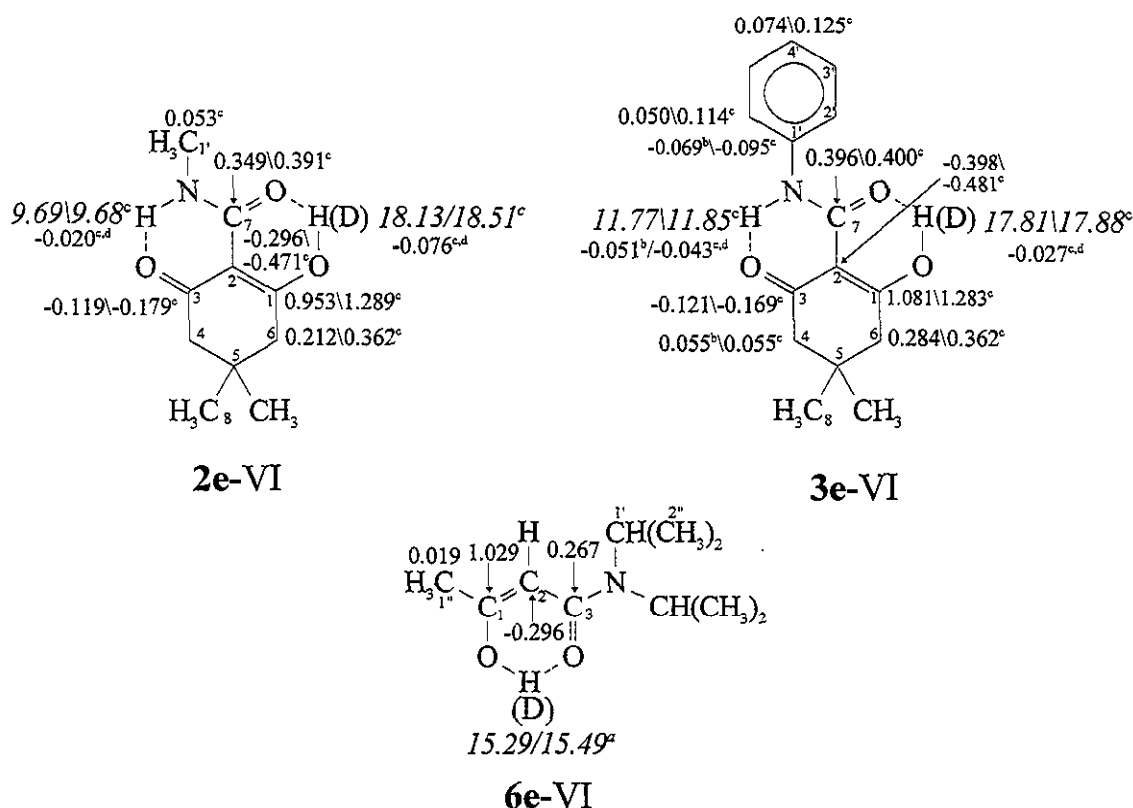


Figure 27. $\Delta C(OD)$, $\delta(NH)$ and $\delta(OH)$ (italic) in ppm for enolic β -ketoamides at 300K in $CDCl_3$, (for $\Delta C(ND)$ see Paper VI). The dominating form in $CDCl_3$ is shown. a: 220K, b: 250K, c: 200K d: Isotope effects on 1H chemical shifts. (Paper VI).

3.3.4 Enolic β -ketothioamides

The large isotope effects of opposite signs at the 'C-OH' and 'C=S' carbons, combined with the large amount of long-range isotope effects, clearly show that the enolic thioamides of 1,3-indandiones (**18e-VI** and **19e-VI**) are tautomeric (figure 28). This is further supported by the change in isotope effects as a function of temperature. For **19e-VI** the sum of $\Delta C-1(XD)$ and $\Delta C-8(XD)$ is -0.912 ppm and -1.059 ppm at 220K and 250K respectively. This sum is very different than observed for enolic β -diketones, due to the large negative isotope effects observed on C-8. The very large negative effect at C-8 for **19e-VI** can be explained by the large chemical shift difference between the C=S and the C-SH carbon resonance. This is found for the enolic β -thioxoketones as well.⁸⁸ The C-1 enolic thioamide form is dominating as seen from the large negative isotope effect on C-8 for **19e-VI**. Five-membered ring enolic

β -diketones **15-V** - **19-V**, **24-V** and **25-V** prefer the exocyclic double bond form, whereas the enolic five-membered ring β -ketothioamide compounds, **12e-VI**, **18e-VI** and **19e-VI** prefer the endocyclic double bond form.

Enolic 1,3-indandiones thioamides is found to be tautomeric, for the five- and six-membered ring enolic ketothioamides the situations are different. The sum of $^2\text{C}(\text{OD})$ and $^4\Delta\text{C}(\text{OD})$ on 0.4 - 0.5 ppm is very low. This suggests that these compounds are non-tautomeric or that the equilibrium is shifted far in the direction of the C-1 enolic form. The temperature dependence on C-1 is 5.5×10^{-4} and 4.6×10^{-4} for **16e-VI** and **12e-VI**, respectively. Comparing this with 1.9×10^{-3} on C-1 and -6.8×10^{-3} on C-8 for **19e-VI**, indicates that the five- and six-membered ring enolic β -ketothioamides as **12e-VI** and **16e-VI** are non-tautomeric.

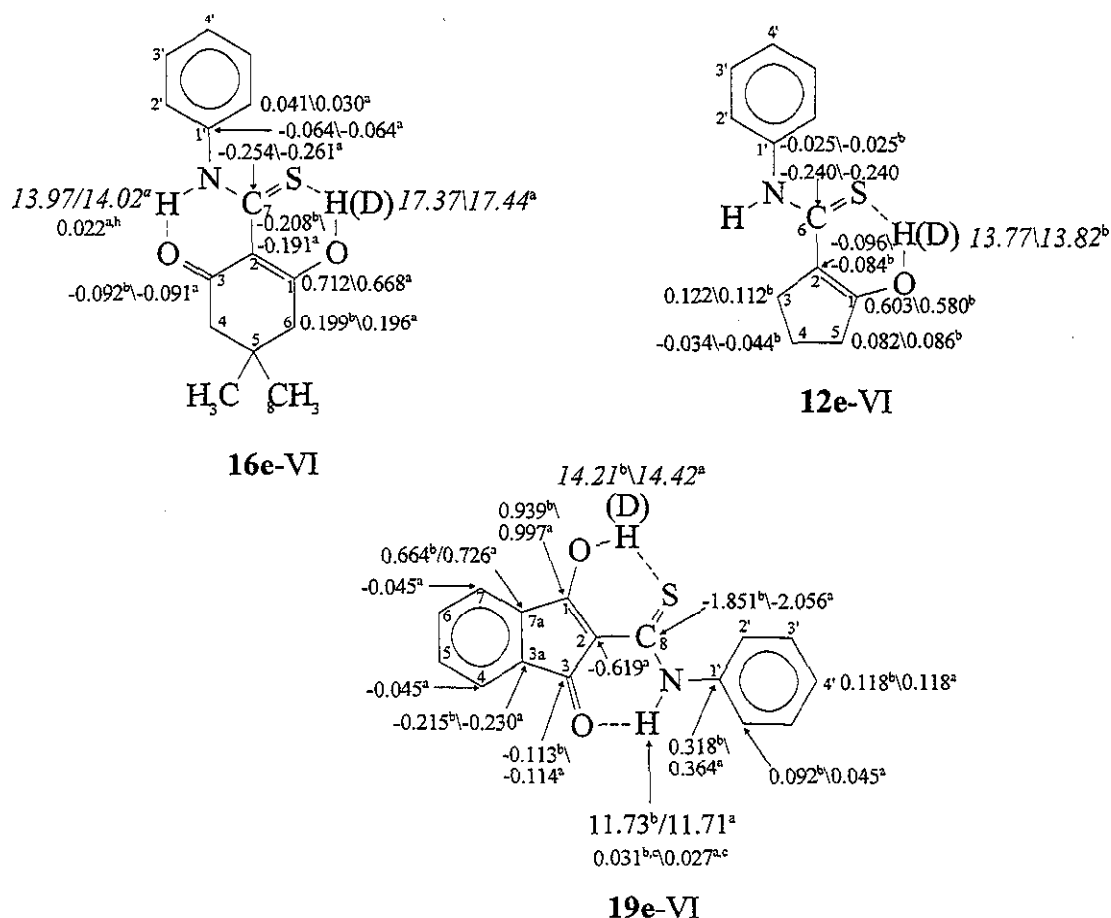


Figure 28. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$, $\delta(\text{SH})$ and $\delta(\text{NH})$ (italic) in ppm. The dominating form in CDCl_3 is shown. a: 220K, b: 250K, c: Isotope effects at the ^1H chemical shifts. (Paper VI).

A large difference is observed when compared the isotope effects on C-1' for **12e-VI** and **16e-VI** of -0.025 and -0.064, respectively, with the isotope effects of 0.318 on C-1' for **19e-VI**. This large difference further indicates that **12e-VI** and **16e-VI** are non-tautomeric and **19e-VI** is tautomeric.

Hydrogen bonds with SH donors are much weaker than hydrogen bonds with OH donors.¹⁰¹ For **12e-VI**, the endocyclic double bond can be stabilised by forming a hydrogen bond with OH as a donor compared with forming an exocyclic double bond and a hydrogen bond with SH as donor. This is presumably the reason that **12e-VI** only exist on one form.

3.3.5 Enolic α -acyl- β -diketones

The large isotope effects and their temperature variations for the enolic α -acyl- β -diketones **1 - 8-X**, (examples shown in figure 29) leave little doubt that these compounds are tautomeric, according to earlier findings.³⁰

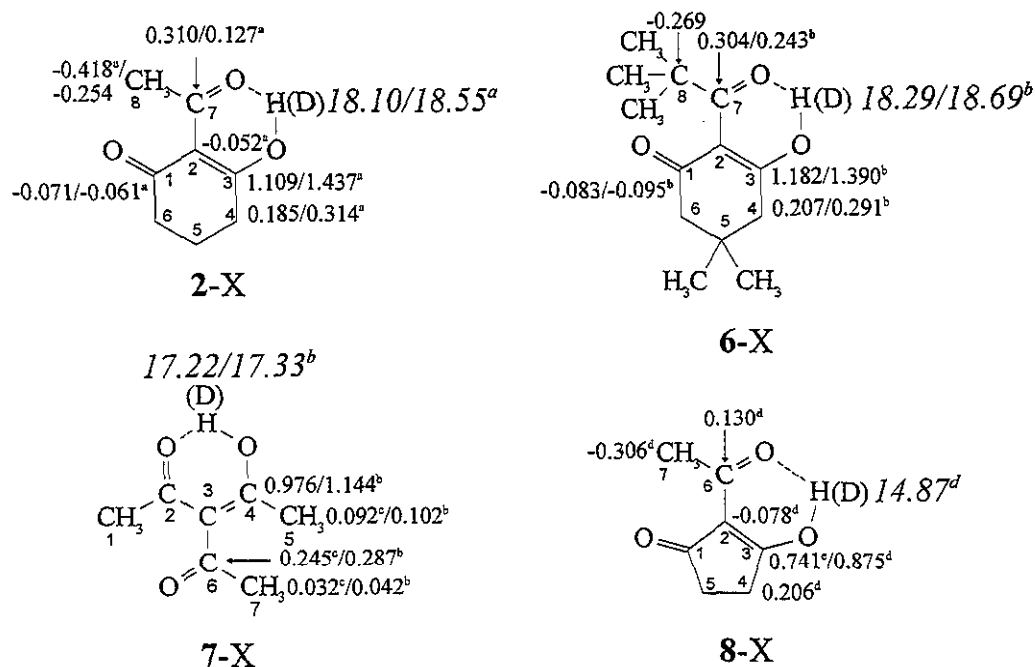


Figure 29. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (italic) in ppm for enolic α -acyl- β -diketones at 300K in CDCl_3 . The dominating form in CDCl_3 is given. a: 220K, b: 230K, c: 260K, d: 170K, e: 190K. (Paper X).

This is also confirmed by couplings from the hydroxy hydrogen to C-3 of 4.6 Hz and 4.8 Hz, and to C-7 of 3.0 Hz and 2.6 Hz for **2-X** and **4-X**, respectively.¹⁰⁰ Only small changes are observed in the isotope effects, when changing the 2-acyl group from acetyl, **2-X** and **3-X** to pivaloyl, **6-X**, which indicates that no steric hindrance is present, even though this might have been expected.

The five-membered ring structure offers a less favourable hydrogen bond which is why smaller isotope effects are found for **8-X** compared with **2-X**. The isotope effect on C-3, for **8-X** suggests that the C-3 enolic form with an endocyclic double bond (Figure 29), is the dominating. This is unusual as five-membered ring systems normally prefer the exocyclic double bond structure⁹⁸ as seen for enolic β -diketones. Preference for the endocyclic double bond form was also observed for enolic β -ketothioamides **12e**, **18e** and **19e-VI**, **12e-VI** is non-tautomeric. These enolic β -ketothioamides, except **12e**, do also have an acyl group in the α position, which indicates that this is the reason for the preferred endocyclic double bond form.

A comparison of $\delta(\text{OH})$ and the sum of $\Delta\text{C-OH(D)}$ and $\Delta\text{C=O(D)}$ for the enolic α -acyl β -diketones (**1 - 8-X**) with the values observed for enolic β -diketones (**1 - 25-V**), shows that the sum is unaffected by the acyl group in the α position. The $\delta(\text{OH})$ has increased ~ 2 ppm due to the acyl group in the α position. This suggests an unaffected hydrogen bond strength and an increase in acidity of the OH proton for the α -acyl substituted compounds. This increase in acidity is also observed for enolic β -ketothioamides with an acyl group in the α position, see **13e-VI** and **16e-VI** paper VI.

3.3.6 Enolic 5-acyl 1,3-dimethylbarbituric acids

The large isotope effect on C-7 for enolic 5-acyl 1,3-dimethylbarbituric acids, **14 - 16-X**, figure 30, show that enolic 5-acyl 1,3-dimethylbarbituric acids prefer the C-7 enolic forms with an exocyclic double bond. The large isotope effects on C-5, C-8, carbonylic C-6 and enolic C-7 clearly demonstrate that the enolic 5-acyl 1,3-dimethylbarbituric acids are tautomeric. The sum of $\Delta\text{C-6(OD)}$ and $\Delta\text{C-7(OD)}$ at ~ 1.5 ppm also strongly suggest a tautomeric system. An isotope effect of -0.12 ppm at 300 K and -0.194 ppm at 200 K for **15-X** are observed at C-9. Such effects in an aliphatic moiety four bonds away from the site of exchange are only observed for tautomeric system. The isotope effect on C-2 is unusual due to

the amide nitrogen between the site of exchange and the carbon in question. The hydroxy hydrogen coupling constant to C-6 and C-7 for **16-X** of 1.9 Hz and 5.3 Hz also shows that the enolic 5-acyl 1,3-dimethylbarbituric acids are tautomeric.

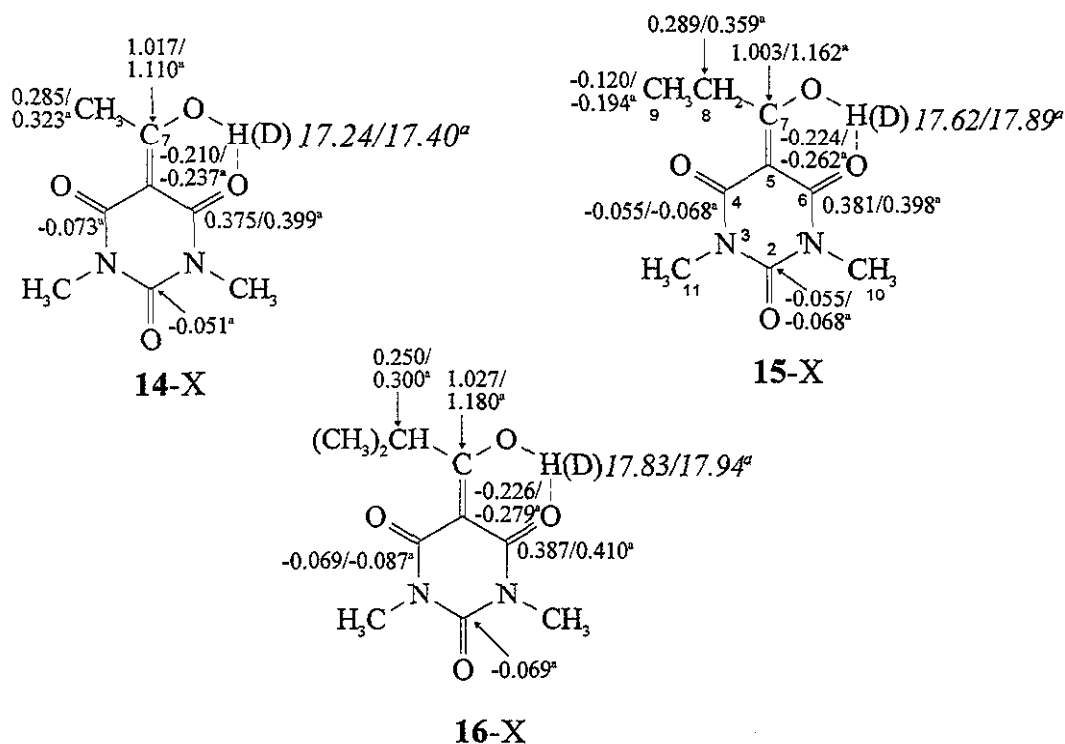


Figure 30. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (italic) in ppm, at 300K in CDCl_3 . The dominating form in CDCl_3 is shown. *a*: 200K. (Paper X).

The enolic 5-acyl 1,3-dimethylbarbituric acids and the enolic β -ketoamide **1e** - **3e-VI** is very alike. Both are β -ketoamides with an acyl group in α position. By interchanging N-1 and CH_3 -8 in **14-X** a structure similar to **2e-VI** is obtained (figure 27). Therefore it is not surprising that the isotope effects in pairs of C-6 for **14-X**, C-7 for **2e-VI**; C-7 for **14-X**, C-1 for **2e-X** and C-8 for **14-X**, C-6 for **2e-VI** are nearly identical. From this is it clear that the amide carbon to a large extend prefers the carbonyl form, and that the position of the amide function determine whether the endo- or the exocyclic double bond form is dominating.

3.3.7 Enolic 5-acyl meldrum acids

It is not trivial to determine whether enolic 5-acyl meldrum acids, (figure 31) are tautomeric or non-tautomeric, even though deuterium isotope effects on ^{13}C chemical shifts are used.

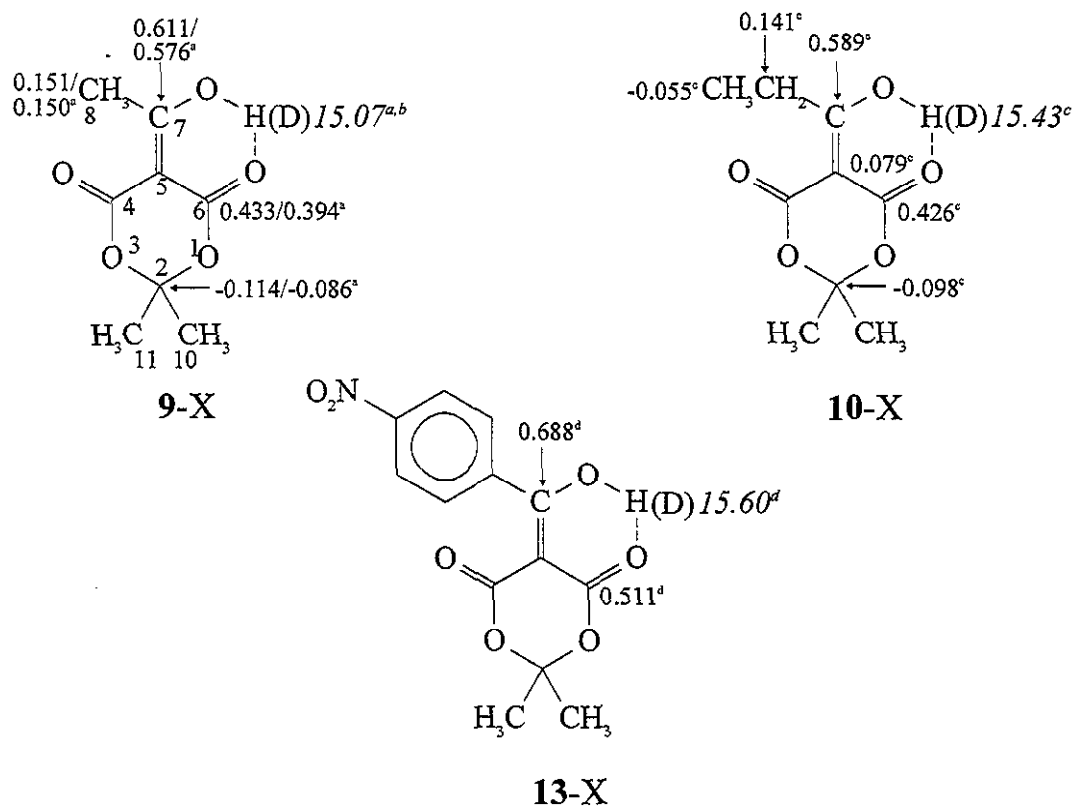


Figure 31. Deuterium isotope effects on ^{13}C chemical shifts and $\delta(\text{OH})$ (italic) in ppm at 300K in CDCl_3 . The dominating form in CDCl_3 is shown. a: 200K, b: 300K, c: 230K, d: 220K. (Paper X).

The temperature dependence on the isotope effects is smaller for enolic 5-acyl meldrum acids than for enolic 5-acyl 1,3-dimethylbarbituric acids and enolic β -diketone systems, showing a non-tautomeric system. The isotope effects on C-7 for enolic 5-acyl meldrum acids, shows that this carbon is enolic. Isotope effects on ^{13}C chemical shifts for enolic β -ketoester is in general smaller than for enolic β -diketones.⁶⁵ If the isotope effects are interpreted as if 5-acyl meldrum acids are non-tautomeric, a $^2\Delta\text{C-7(OD)}$ of ~ 0.6 ppm is obtained. This is a large two bond isotope effect, but such effects have been observed for ketones.⁶⁶ Thence, the isotope effect on C-6 is a four-bond isotope effect, and a four-bond isotope of 0.4 - 0.5 ppm has never been observed in non-tautomeric systems. The isotope effect on C-2, as seen for 9-X and 10-X (figure 31), is very unusual, due to the ester oxygen between the site of deuterium and the carbon in question. The isotope effect on C-2 is, in a non-tautomeric system, a six-bond effect in the order of ~ -0.1 ppm, which has never been seen for esters. The coupling from the

hydroxy hydrogen to C-6 is not observed for **10-X**, which means that this coupling constant is less than 1 Hz. The coupling to C-7 is 5.7 Hz.¹⁰⁰ This shows that 5-acyl meldrum acid is on C-7 enolic forms, and that the C-6 enolic form is absent or only slightly present. From the present data, the 5-acyl meldrum acid system is believed to be tautomeric. The tautomeric equilibrium is shifted far in favour of the exocyclic form.

3.4 Deuterium isotope effects on ^{19}F chemical shifts

Deuterium isotope effects on ^{19}F chemical shielding are determined in intramolecular hydrogen bonded compounds, counting fluorinated *o*-hydroxy acyl aromatic, enaminones, *o*-hydroxy azo and hydrazo compounds. The latter represent both tautomeric and non-tautomeric cases.

A parallel behaviour in sign and magnitude is observed for $^{n+1}\Delta\text{F(OD)}$ and $^n\Delta\text{C(OD)}$ for the *o*-hydroxy acyl aromatic compounds **1 - 7-VIII**, **9-VIII** and **10-VIII**. This shows either that $\Delta\text{F(OD)}$ depends on the isotope perturbations in fashion different from $\Delta\text{C(OD)}$ or that the alternation suggested for $\Delta\text{C(OD)}$ ^{74,86} is shifted one bond for fluorine.

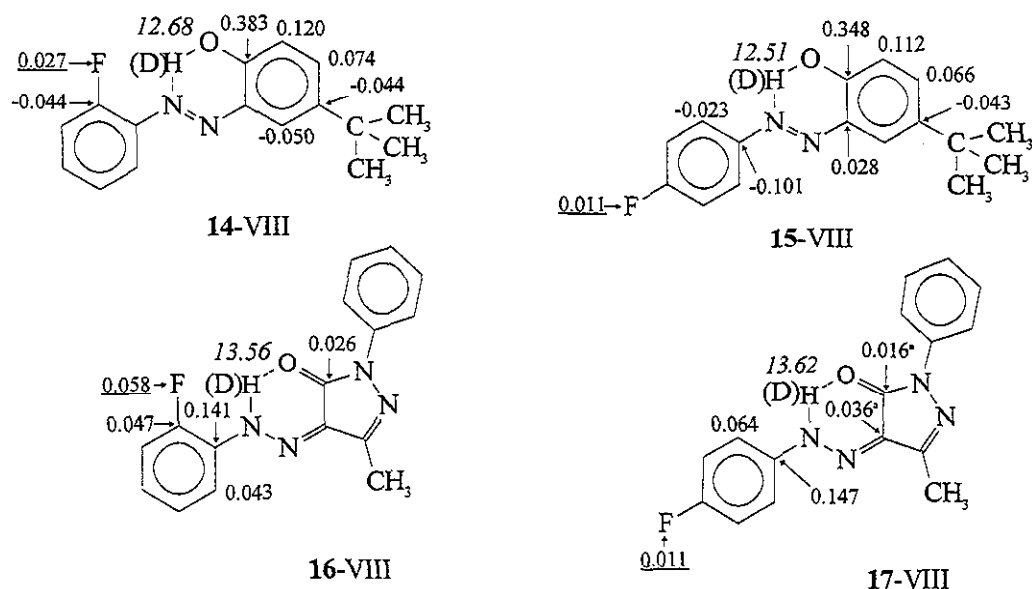


Figure 32. $\Delta\text{C(XD)}$, $\Delta\text{F(XD)}$ (*underlined*) and $\delta(\text{OD})$ and $\delta(\text{ND})$ (*italic*), in ppm, at 300K in CDCl_3 for non-tautomeric **14 - 17-VIII** compounds. *a*: 230K. (Paper VIII).

Compound **22**, **23** and **25-VIII** are earlier shown to be tautomeric.^{93,94} The large negative isotope effects on C-1 for **24-VIII**, C-2 for **22-VIII** and **23-VIII** indicates tautomerism. For **25-VIII** the isotope effect on C-1 is positive and has a value of 0.058 ppm. This small positive effects can be explained if the contributions from the equilibrium isotope effects are negative, as seen on C-1 for **24-VIII** and of approximately the same magnitude as the intrinsic isotope effects. The large isotope effects observed throughout the N-phenyl group and on C-6, which is seven or eight bonds away from the site of deuterations, shows that these compounds are tautomeric.

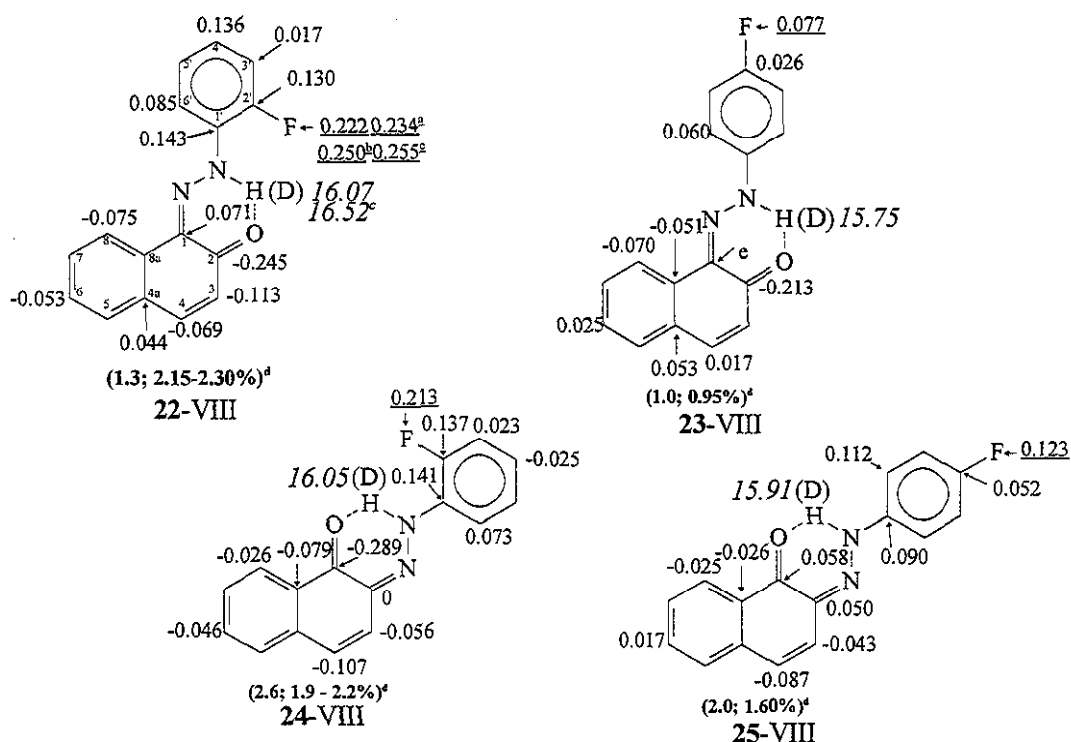


Figure 33. $\Delta C(XD)$, $\Delta F(XD)$ (*underlined*) and $\delta(XD)$ (*italic*), in ppm, at 300K in $CDCl_3$ for tautomeric **22** - **25-VIII** compounds. a: 280K, b: 250K, c: 225K, d: The equilibrium constant, $K = [\text{hydrazo}]/[\text{azo}]$, and the change in the equilibrium upon deuteration, ΔX_D , is given in brackets, e: Not observed. The dominating form in $CDCl_3$ is given. (Paper VIII).

The large values of $\Delta F(XD)$ observed for **22-VIII**, **24-VIII** and **23-VIII** - **25-VIII** compared with **14-VIII** - **16-VIII** and **15-VIII** - **17-VIII**, respectively, shows that **22** - **25-VIII** is tautomeric. $\Delta F(XD)$ for **22-VIII** was found temperature sensitive, also shows that this system

is tautomeric.

The small intrinsic contributions to the observed isotope effects on fluorine, as seen for the non-tautomeric *o*-fluorine (**14-VIII**, **16-VIII**) and *p*-fluorine (**15-VIII**, **17-VIII**), makes $\Delta F(XD)$ a very suitable probe for tautomerism. From these an estimations of the change in equilibrium upon deuteration is possible.

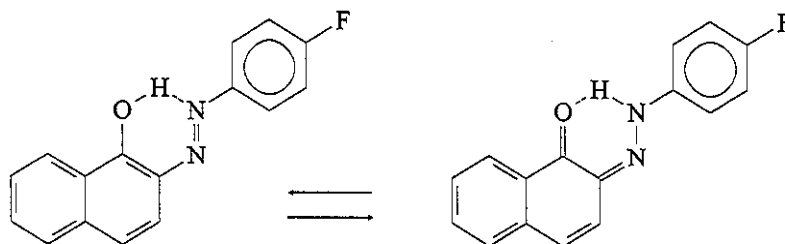


Figure 34. Azo - hydrazone tautomerism shown for **25-VIII**.

For the azo - hydrazone tautomerism, figure 34, the mole fraction of hydrazone, is estimated from $\delta^{19}\text{F}$ using the relation given in eq. 12.⁹⁴

$$\% \text{ Hydrazone} = \frac{\delta(^{19}\text{F})_2 - \delta(^{19}\text{F})_x}{\delta(^{19}\text{F})_2 - \delta(^{19}\text{F})_1} \cdot 100\% \quad (\text{eq. 12})$$

$\delta(^{19}\text{F})_x$ represents the fluorine chemical shifts of the compound in question, **22 -VIII - 25-VIII**. $\delta(^{19}\text{F})_1$ and $\delta(^{19}\text{F})_2$ denotes the fluorine chemical shifts of the hydrazone forms **16-VIII**, **17-VIII** and the azo forms **14-VIII**, **15-VIII**.

The changes in the equilibrium constants or mole fractions upon deuteration, given in figure 33, are estimated from equation 13, stated for **24-VIII**.

$$\Delta F(XD)_{\text{obs}} = X_{[\text{Hydrazone}]} \times {}^4\Delta F(\text{ND}) + X_{[\text{azo}]} \times {}^8\Delta F(\text{OD}) + \Delta X_D \times (\delta(^{19}\text{F})_2 - \delta(^{19}\text{F})_1) \quad (\text{eq. 13})$$

$X_{[\text{Hydrazone}]}$ is the mole fraction of hydrazone and ΔX_D is the change in mole fraction due to deuteration.

For **22 - VIII - 25-VIII**, ΔX_D vs. X is plotted with the data for the enolic β -diketones (figure 24). Despite the small number of data points, it is likely that the hydrazone - azo tautomerism follows the same pattern as enolic β -diketones.

3.5 Summery of tautomeric systems

The structure element shown in figure 35 can be tautomeric or non-tautomeric.

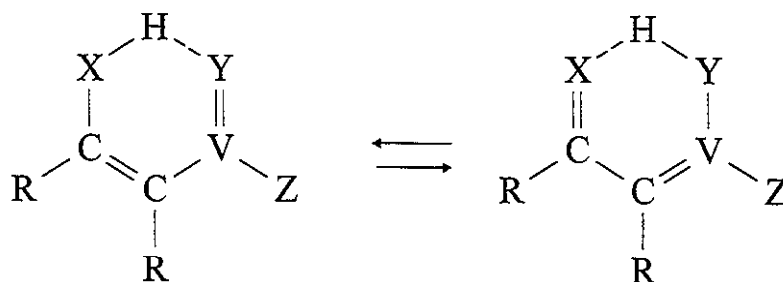


Figure 35. $X = O, S$ or N ; $Y = S$ or O ; $Z = O, S, N$ or C $V = S, N$ or C and $R = H$ or C .

Table 1.

V	X	Y	Z	tau./non-tau ^a	Paper ^b
carbon	oxygen	oxygen	oxygen	non-tau	IV,V,X ^c
carbon	oxygen	oxygen	sulfur	non-tau.	VI
carbon	oxygen	oxygen	nitrogen	tau.	VI,X
carbon	oxygen	oxygen	carbon	tau.	IV,V,X
carbon	oxygen	sulfur	nitrogen	tau.	VI
carbon	sulfur	oxygen	oxygen	non-tau	III
carbon	sulfur	oxygen	sulfur	non-tau	III
carbon	nitrogen	oxygen	oxygen	non-tau	III
carbon	nitrogen	oxygen	carbon	non-tau.	III, IV, VII, VIII
sulfur	nitrogen	oxygen	carbon	non-tau.	III
nitrogen	nitrogen	oxygen	oxygen	non-tau	III
nitrogen	oxygen	nitrogen	lone pair	tau.	VIII
nitrogen	oxygen	oxygen	lone pair	tau.	IX

a: tau. and non-tau means tautomeric and non-tautomeric respectively

b: papers refer to the papers in appendix that deals with this system

c: 1-IV is an exception, $Z = \text{oxygen}$ is part of an anhydride moiety.

Whether a compound is tautomeric or non-tautomeric depends on the atom constitution of the structure element. From the present data this can be tested to some extent. In table 1, the term tautomeric is used for cases where structure elements are found tautomeric in some systems. The term non-tautomeric is used when structure elements are found non-tautomeric in all of the investigated systems.

The data in table 1 shows that for a system to be tautomeric X must be oxygen and Z must not be oxygen or sulfur. Enolic β -thioxoketones are known to be tautomeric.^{88,101} This implies that X also can be sulfur when Y = O and Z = V = C.

4 Conclusions

The present results show that deuterium isotope effects on ^{13}C chemical shifts hold information of the structural features and tautomerism for systems involving intramolecular hydrogen bonds.

It is confirmed that the OH group forms stronger hydrogen bonds than the OD groups for resonance assisted hydrogen bonds.

Two donors competing for one acceptor are shown to weaken the individual hydrogen bonds.

Deuterium isotope effects are shown to reveal steric hindrance and steric compression.

Deuterium isotope effects can be used to determine whether an intramolecular hydrogen bonded system is tautomeric or non-tautomeric. Tautomeric equilibria are shown to be perturbed by the exchange of hydrogen with deuterium, and the degree of perturbations are determined for a series of enolic β -diketones. The perturbations are shown to be largest for tautomeric systems, having a mole fraction of 0.75.

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Paper I

Variable-Temperature NMR Studies of 2,6-Dihydroxy Acylaromatic Compounds. Deuterium Isotope Effects on Chemical Shifts, Isotopic Perturbation of Equilibrium and Barriers to Rotation

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A series of 2,6-dihydroxy acylaromatic compounds were investigated to characterize the rotational and hydrogen bonding properties of the carbonyl group. Deuterium isotope effects on ^1H and ^{13}C chemical shifts due to deuteration of OH groups were determined at both ambient and low temperature. In the latter case isotope effects on chemical shifts of the individual rotamers can be determined. Deuteration of one of the OH groups may lead to isotopic perturbation of the tautomeric equilibrium of the carbonyl group and the two hydroxyl groups. The perturbation was found to be larger in ketones than in esters. Complete band shape analysis of the OH resonances of the esters and ketones in a temperature interval above and below the coalescence temperature led to ΔG^\ddagger , AH^\ddagger and ΔS^\ddagger values for various concentrations of added THF- d_6 . ΔS^\ddagger was found to be strongly negative. Temperature coefficients for the shift of the OH resonances showed large variations for esters and ketones owing to the different hydrogen bond patterns. The esters have two intramolecular hydrogen bonds, one strong and an additional weaker one between the OH and OR groups. The second OH group of the ketones was shown to point primarily towards C-5. Increasing amounts of THF- d_6 increased the amount of this rotamer. The anisotropy of the $\text{XC}=\text{O}$ group at C-2, C-6 was shown to lead to a low-field shift of C-2, very different from that found for $\text{C}=\text{O}$ groups without hydrogen bonds. The anisotropy caused by OH groups can also be estimated. On the basis of the thermodynamic parameters, a model for the rotation of the ester group is suggested. The rate-determining step involves both intramolecular hydrogen bonds, which are twisted out of the ring plane to form hydrogen bonds to the solvent or other hydrogen bond acceptors.

KEY WORDS ^{13}C NMR Deuterium NMR isotope effects Rotational barriers *o*-Hydroxy acylaromatics
Isotopic perturbation of equilibrium Band shape analysis

Paper II

Deuterium and ^{18}O Isotope Effects on ^{13}C Chemical Shifts of Sterically Hindered and/or Intramolecularly Hydrogen-Bonded *o*-Hydroxy Acyl Aromatics

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A series of sterically hindered *o*-hydroxy aromatic ketones were synthesized, including benzene, naphthalene, phenanthrene and pyrene derivatives. Deuterium isotope effects on the ^{13}C chemical shifts of 2-hydroxy-1-acenaphthone and other sterically hindered, intramolecularly hydrogen-bonded aromatic ketones (OH exchanged) are shown to be unusual. The two-bond isotope effects are very large. Likewise are the isotope effects on C=O, C-1, C-3 and C-4 carbon resonances and some show unusual signs. These unusual effects are explained by a higher degree of twist in the deuterio than the protio compound. Steric isotope effects are also observed on OH chemical shifts of sterically hindered *o*-hydroxy acetyl aromatic compounds deuteriated at the methyl group. These isotope effects show non-additivity. For one-bond isotope effects, $^1\Delta^{13}\text{C}(^{18}\text{O})$, hydrogen bonding leads to a decrease, whereas twisting of the carbonyl group leads to an increase. Two hydrogen bonds to the same acceptor has a reduced cumulative effect. Data for sterically hindered, hydrogen-bonded compounds are found to fall outside the correlation between $\delta(^{17}\text{O})$ and $^1\Delta^{13}\text{C}(^{18}\text{O})$.

KEY WORDS NMR NMR Isotope effects on ^{13}C chemical shifts Deuterium isotope effects ^{18}O isotope effects Intramolecular hydrogen bonding Steric strain Hydrogen bond strength

Paper III

Deuterium Isotope Effects on ^{13}C Chemical Shifts of Intramolecularly Hydrogen-Bonded Olefins

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A series of intramolecularly hydrogen-bonded enamines, enols and enethiols with ester carbonylic, ketonic carbonylic, thioester carbonylic, nitro and sulfoxide acceptors were investigated to obtain ^{13}C chemical shifts and deuterium isotope effects. Results from 33 new compounds and six remeasurements are compared with already existing data. An important aim was to show that isotope effects on chemical shifts are useful descriptors of hydrogen-bonded systems and not only a parameter proportional to the ^{13}C chemical shifts. Substituent effects were studied and the donors and acceptors ranked according to their abilities to support hydrogen bonding. Steric effects strengthen the hydrogen bonding in cyclic five-membered β -diketones. Plots of two-bond $[^2\Delta\text{C}(\text{OD})]$ vs. four-bond isotope effects $[^4\Delta\text{C}(\text{OD})]$ show that $^4\Delta\text{C}(\text{OD})$ increases with increasing hydrogen bond strength and that large deviations from this relationship can be an indicator of tautomerism.

KEY WORDS NMR; ^{13}C NMR; isotope effects on ^{13}C chemical shifts; deuterium isotope effects; intramolecular hydrogen bonding; hydrogen bond strength; olefins; β -sulphinylenamines; nitroenamines; β -diketones (five-membered ring)

Paper IV

Intramolecular hydrogen bonding and tautomerism of acylpyran-2,4-diones, -2,4,6-triones and acylpyridinediones and benzannelated derivatives. Deuterium isotope effects on ^{13}C NMR chemical shifts

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The structures of acylpyran-diones, -triones and acylpyridinediones have been studied primarily by deuterium isotope effects on ^{13}C chemical shifts. The 3,5-diacetyltetrahydropyran-2,4,6-trione forms a double tautomeric system involving one of the carbonyl carbons of the anhydride moiety. This compound also exists as a minor symmetrical isomer with two intramolecular hydrogen bonds to the same acceptor. This isomer shows isotopic perturbation of the OH proton resonance upon deuteration. A similar situation is found for 1,5-diphenylpentane-1,3,5-trione.

The 3-acetyl-6-methyl-2H-pyran-2,4(3H)-dione is found to be tautomeric and mainly in the 4-hydroxy form. The corresponding 5-acetyl derivative forms a very weak hydrogen bond as is also found in the 5-ethoxycarbonyl-6-methylpyridine-2,4(3H)-dione. The same pattern is found for 3- and 5-acetyl-6-methylpyridine-2,4(3H)-dione. This difference in the two-bond deuterium isotope effect is related to the bond orders of the bonds linking the hydrogen bond donors and acceptors and reflects the strength of the intramolecular hydrogen bonds. The 3-acetyl-4-hydroxy-2(1H)-quinolones are tautomeric in a similar fashion.

The formal hydroxypyridines are shown by isotope effects to be of the 2-pyridone form.

The formal imines of most of the above compounds have also been studied and are shown to exist in their keto-enamine forms. In the case of 3-(1-amino)ethylidenequinoline-2,4(1H,3H)-diones and 2-(1-amino)ethylidene-6,7-dihydro-5H-benzo[*ij*]quinolizine-1,3(2H)-diones two different forms with hydrogen bonds to either the carbonyl at C-4 or the amide carbonyl group at C-2 are observed. Deuterium isotope effects on chemical shifts again turned out to be crucial in the structure elucidation.

Paper V

Deuterium-Induced Isotope Effects on ^{13}C Chemical Shifts as a Probe for Tautomerism in Enolic β -Diketones

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Deuterium isotope effects on ^{13}C nuclear shielding, $\Delta C(\text{OD})$, were investigated for a series of enolic β -diketones at different temperatures. The investigated enolic β -diketones cover a broad range of tautomeric equilibrium constants (K). The equilibrium constants were estimated from ^{17}O and ^{13}C chemical shifts. ^{13}C chemical shifts and the deuterium isotope effects show changes with temperature, which are due to a change in the tautomeric equilibrium. It is shown that the variation of K with deuterium substitution depends on K . This has the important consequence that the equilibrium isotope effects for a series with different K may go through a maximum. If the sum of the deuterium isotope effects on ^{13}C chemical shifts for the carbonyl and enolic carbons is above 0.8 ppm for five-membered and 1.2 ppm for six-membered ring compounds, the system is tautomeric. This statement holds for sterically non-hindered compounds. The intrinsic two-bond deuterium isotope effects for an intramolecular hydrogen bonded system with a chelate six-membered ring with optimal geometry and a localized double bond are estimated to be 1.2 ppm. Knowing the intrinsic contribution, deuterium isotope effects can be used to estimate the position of tautomeric equilibria for β -diketones. ^1H chemical shifts of OH groups display a linear relation with the molar fraction X .

KEY WORDS NMR; ^{13}C NMR; isotope shifts; ^2H isotope effects; equilibrium isotope effects; enolic β -diketones; tautomeric equilibria

Paper VI

Intramolecular hydrogen bonding of the enol forms
of β -ketoamides and β -ketothioamides.
Deuterium isotope effects on ^{13}C chemical shifts¹

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Abstract

Deuterium isotope effects of ^{13}C chemical shifts are studied in a series of enol and keto forms of β -ketoamides and the corresponding thioamides. In addition, the 2,6-cyclohexanediketo-1-amides and thioamides are studied. The effects of ring size (five- and six-membered rings) on the isotope effects and the tautomeric nature of the systems are also looked into. Rather unusual isotope effects are found for the amides, indicating a tautomeric system of the $-\text{C}=\text{ONHRCOHNHR}$ type. This is supported by the ^{17}O chemical shift studies.

The isotope effects of the simple amides are compared with those of the tetracyclines and piroxicams.

The study of *N*-phenyl-3-phenyl-3-oxo-propiothioamide at low temperature reveals that this thioamide exists as a mixture of *s*-cis and *s*-trans species. The isotope effects and the influence of intramolecular hydrogen bonding in the two species can thus be studied.

Thioamides of indan-1,3-diones show tautomeric behaviour, as revealed by very large deuterium isotope effects of both signs. Deuteriation shifts the equilibrium in the direction of the thioamide.

Finally, the tendency of a series of β -hydroxy esters, thioesters, anhydrides, amides, thioamides, aldehydes and ketones to become tautomeric is discussed in terms of hydrogen bonding, isotope effects, $^2\Delta\text{C}(\text{OD})$, and the nature of the acceptor.

Keywords: Isotope effect; NMR spectroscopy; β -Ketoamide; β -Ketothioamide

Paper VII

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Deuterium Isotope Effects on ^{13}C Chemical Shifts of Enaminones

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ABSTRACT

Deuterium isotope effects on ^{13}C chemical shifts are studied in a series of substituted N-alkyl and N-phenyl keto-enamines. The intramolecularly hydrogen bonded Z-forms show the largest two-bond isotope effects, $^2\Delta\text{C-1(ND)}$. Methyl substitution at C-1 leads to a larger two-bond isotope effect in the N-phenyl substituted derivatives. This effect is ascribed to steric compression. Space filling substituents at the o-position of the N-phenyl ring leads to a decrease of the two-bond isotope effect. A correlation is found between $^2\Delta\text{C-1(ND)}$ and $^3\Delta\text{C-2'(ND)}$. The latter becomes negative in the sterical hindered cases. $^3\Delta\text{C-2'(ND)}$ may therefore be used as a gauge of the twist of the phenyl ring.

o-Hydroxy substitution of the CO-phenyl rings enables intramolecular hydrogen bonding to the carbonyl group. This kind of hydrogen bonds with two donors to one acceptor leads to smaller $^2\Delta\text{C-2(ND)}$ and $^2\Delta\text{C-2''(OD)}$ isotope effects equivalent to weaker hydrogen bonds for the Z-isomer. This is ascribed to competition for the acceptor. For the E-isomer the $^2\Delta\text{C(OD)}$ is enhanced. The same feature is seen for N,N-dimethylaminoenamines. This increase is ascribed to delocalization of the nitrogen lone-pair onto the carbonyl oxygen, thereby strengthening the hydrogen bond and thus leading to larger two-bond, $^2\Delta\text{C(OD)}$, isotope effects.

INTRODUCTION

Keto-enamines are a class of compounds with unusual features concerning the E:Z ratio.¹ The ratio is clearly dependent on the solvent and could possibly be related to hydrogen bonding. This feature is not yet fully clarified. The Z-form shows intramolecular hydrogen bonding. This feature can with advantage be studied by means of deuterium isotope effects on ^{13}C chemical shifts.²⁻¹⁷ These isotope effects in intramolecularly hydrogen bonded olefins show interesting relationships between $^2\Delta\text{C(ND)}$, δNH and $\delta\text{C-1}$ or $\delta\text{C-2}$.⁴ Of interest is also the increase in $^2\Delta\text{C(ND)}$ with N-phenyl substitution.^{3,11-13}

The present compounds enables a study of the effect of substitution of the phenyl rings at the nitrogen (ring A (Fig. 1)) or at the phenyl rings at the carbonyl group (ring B) as well as substitution at C-1.

Intramolecular hydrogen bonding with two hydrogen bond donors to one acceptor is of much interest. This has been studied in $\text{OH}\dots\text{C}=\text{O}\dots\text{HO}$ cases both by means of $^n\Delta\text{C(D)}$

and $^{13}\text{C}(^{18}\text{O})$ isotope effects.^{10,16} OH groups in *o*-position of the B phenyl rings enables formation of this kind of dual donors to one carbonyl groups, and with the two different donors, OH and NH.

Deuterium isotope effects have been studied in detail in *o*-hydroxy acyl aromatics.^{8,14,16} The exact mechanism of these effects are not fully clarified although a dominant feature of these isotope effects is the importance of resonance assisted hydrogen bonding (RAHB).^{14,16} RAHB can be divided into three parts, the intervening double bond, the acceptor and the donor.⁴ Some of the present compounds enables an estimation of the importance of charges at the acceptor atom.

RESULTS

Deuteriation is normally done by treatment of the compounds with a mixture of CH_3OD and CH_3OH followed by evaporation and dissolving the deuterated compound in the NMR solvent or by dissolving the compounds in CDCl_3 and stirring the solution with a mixture of $\text{H}_2\text{O}:\text{D}_2\text{O}$ followed by drying. For compounds dissolved in $\text{DMSO}-d_6$ deuteriation is done by addition of a mixture of $\text{H}_2\text{O}:\text{D}_2\text{O}$. The degree of deuteriation can be varied in all three methods. Variation of the H:D ratio is used to assure the signs of the isotope effects. As all the compounds are unsubstituted at C-2, deuteriation may also take place at this position in addition to the NH group or at the OH position for compounds **5**, **9** and **30-32**. As the exchange rates for exchange at C-2 and at NH are different, isotope effects due to deuteriation at the two sites can be differentiated, especially using mixtures of $\text{H}_2\text{O}:\text{D}_2\text{O}$ for deuteriation. The three types of isotope effects are called $^n\Delta\text{C}(\text{ND})$, $^n\Delta\text{C}(\text{OD})$ and $^n\Delta\text{C}(\text{D})$ and are the result of deuteriation at NH, OH or C-2 positions. The isotope effects are defined as $^n\Delta\text{C}(\text{D}) = \delta\text{C}(\text{H}) - \delta\text{C}(\text{D})$.

The compounds occur exclusively as the *Z*-form in CDCl_3 , whereas in $\text{DMSO}-d_6$ the compounds (**1-9**, **17**, **18**, **28**) appear on both forms. This feature has previously been studied.^{1,18}

The ^{13}C chemical shifts are given in Table 1. The assignments are based on substituent effects.

Some of the ^1H and ^{13}C chemical shifts have previously been published.^{1,19,20} The deuterium isotope effects and XH chemical shifts are given in Scheme 1.

Isotope effect are not observed for all *E*-forms. In **4** and **5** the ^{13}C resonances of the deuteriated species are broad and for **2** and **9** the *E*-isomer is not very abundant. Despite the indication of rather strong hydrogen bonds (large $^2\Delta\text{C}-2''(\text{OD})$) the OH resonances of **5E** and **9E** and **31** are broad at room temperature and only the very large $^2\Delta\text{C}-2''(\text{OD})$ isotope effects are observed. The broadness of the ^{13}C resonances is probably related to OH and NH exchange as it is disappearing for **31** at lower temperature. The variation in $^2\Delta\text{C}-2''(\text{OD})$ between **30** and **31** is remarkable as this parameter is very similar for the corresponding 5-fluoro- and di-3,5-difluoro-2-hydroxyacetophenones.¹⁴

Intramolecular hydrogen bonding has a profound effect at $^2\Delta\text{C}-1(\text{ND})$ as seen in Scheme 1 comparing the data for *E*- and *Z*-compounds. The isotope effects for the *E*-

compounds do not vary very much as also found previously.³

Data in the two solvents, CDCl_3 and DMSO-d_6 , are generally similar for the investigated compounds, something that is found to hold for compounds with medium strong hydrogen bonds.^{14,15}

For the Z-compounds N-phenyl substitution leads to an increase in $^2\Delta\text{C-1(ND)}$ and in δNH as seen by comparison of compounds **1Z** and compounds **2 - 11** and **14 - 29** in general (Scheme 1) with those of **12** and **13** (see also Fig. 3). This feature has also been observed in a few keto- and nitroenamines.³ The origin of this effect can possibly be clarified by the study of derivatives with substituents at the phenyl ring. As seen in Fig. 3 substitution at the para-position of the A-ring with an electron attracting substituent leads to an increase of $^2\Delta\text{C-1(ND)}$, whereas electron donating substituents have the opposite effect. The effect at δNH is small and no regular pattern is seen.

Methyl substitution at C-1 led to a small increase of $^2\Delta\text{C(ND)}$ of a $\text{NH}(\text{CH}(\text{CH}_3)_2)$ derivative.³ In the compounds with phenyl substitution at nitrogen the increase in $^2\Delta\text{C-1(ND)}$ is clearly much larger (**10,11,15, 24 - 29**) (see Fig. 3). It is also interesting to notice that a phenyl group at C-1 (**14**) has only a small effect. A difference in the chemical shifts of e.g. C-2, C-4' or between C-6' between compounds with and without a methyl substituent at C-1 (Table 1) is also found. The increase in $^2\Delta\text{C-1(ND)}$ can roughly be related to the ^{13}C chemical shift of the C-1 carbon as seen by a comparison of this with the two-bond isotope effects for **1Z, 10Z, 15** and **29**.

Strong steric hindrance is introduced in compounds like **26** and **27**, in which steric hindrance of the phenyl group leads to twist of this and a concomitant reduction of $^2\Delta\text{C-1(ND)}$. Such a reduction was even seen for **2Z** in which the OH group at the 2'-position probably leads to a similar effect. An interesting effect was observed in **26** and **27**. The negative three-bond isotope effects at C-2' and C-6' and a negative five-bond effect at C-4'. Smaller than usual effects are also observed in **21 - 23**, but not in **25**. A plot of $^3\Delta\text{C-1(ND)}$ and $^2\Delta\text{C-1(ND)}$ vs. shows a good correlation (Fig. 4). A plot of $^3\Delta\text{C-2'(ND)}$ vs. δNH gave a poorer correlation (not shown) possibly due to anisotropy effect at the NH chemical shift.

The compounds with OH groups in o-position of rings A or B are a special case as they form intramolecular hydrogen bonds to either the carbonyl group or the NH group. An OH substituent in o-position in the A-ring as found in **2** has a decreasing effect at $^2\Delta\text{C-1(ND)}$.

The C-2'(OH) proton is clearly exchanged quickly as no isotope effects due to OD'-2 is seen. This excludes a strong hydrogen bond to the NH nitrogen. However, a weak effect cannot be excluded. The value for **2Z** falls under the line in Fig. 3, supporting the above mentioned.

The isotope effects, $^2\Delta\text{C(OD)}$, observed in **30-32** correspond roughly to the isotope effects found for *o*-hydroxy acyl aromatics⁸ except as mentioned above the isotope effect of **31** and that the isotope effects for C-3 of **30** and **31** do not fall on the δOH vs $^4\Delta\text{C(OD)}$ plot.

DISCUSSION

$^2\Delta\text{C(OD)}$

The **5E** and **9E** derivatives show an interesting increase in $^2\Delta\text{C(OD)}$ as compared to e.g. 2-hydroxychalcone¹⁴ and **32**. This can be ascribed to the effect of the aminosubstituent. This is further confirmed by the observation of large $^2\Delta\text{C(OD)}$ for both **30** and **31**. This effect is related to the negative charge at the carbonyl oxygen caused by delocalization of the enamine-nitrogen lone-pair (Fig.2A).

The compounds **5** and **9** constitute a very useful couple in the investigation of simultaneous intramolecular hydrogen bonding to one acceptor. **5** is soluble enough in CDCl_3 to allow recording of ^{13}C spectra. The compound is almost entirely on the **Z** form in this solvent. The good solubility does also indicate that the OH group is engaged in intramolecular hydrogen bonding. The $^2\Delta\text{C-2''(OD)} = 0.329$ ppm and $^2\Delta\text{C-1(ND)} = 0.285$ ppm in CDCl_3 and very similar values are found in DMSO-d_6 (Scheme 1). A comparison with **6Z** shows a larger $^2\Delta\text{C-1(ND)}$ in the latter. The **5E**- and **9E** isomers gives a much larger $^2\Delta\text{C-2''(OD)}$ than the **5Z**- and **9E** isomers. Both findings are in line with a simultaneous hydrogen bonding leading to weaker hydrogen bonds for both donors.

$^2\Delta\text{C(ND)}$

The finding that the $^2\Delta\text{C(ND)}$ of **E**-derivatives are smaller than for the **Z**-isomer and do not vary very much shows, that the second resonance from (Fig. 2B) is only effective in conjunction with the hydrogen bonds as found in the **Z**-compounds or alternatively in the hydrogen bond between the C=O group and an *o*-OH group as found in **5E,9E, 30** and **31**.

The effect of *p*-substitution at the A-ring is due to lone-pair delocalization of the nitrogen lone-pair into the A-ring leading to increased double bond character of the N-C-1'

bond and a more positively charged nitrogen (Fig. 2B). This also leads to observation of positive long-range isotope effects at C-4, $^5\Delta\text{C-4' (ND)}$, as clearly observed in **15-17**, **20**, but not in **18** in which the substituent is electron donating. A similar trend is seen for the *o*-substituted derivatives **24**, **25** and **28**. The five-bond isotope effects for **17** and **24** are smaller than for **15**. For the strongly sterical hindered compounds **26** and **27**, the effects are negative as explained below. From what is said above it is clear that conjugation is an important factor leading to an increase of the $^2\Delta\text{C-1 (ND)}$ isotope effect.

The methyl group at C-1 causes an increase of $^2\Delta\text{C-1 (ND)}$ of the order of 0.05 ppm for most compounds, but not so for the strongly sterical hindered compounds, **26** and **27**. A small increase in $^2\Delta\text{C-1 (ND)}$ upon methyl substitution at C-1 of N-alkyl enamines is observed.³ For enaminoesters no significant effect on the two-bond isotope effect was found.⁴ The increase in $^2\Delta\text{C-1 (ND)}$ can be seen as the result of two counteracting effects. The methyl group at C-1 both leads to a steric compression of bonds and to a twist of the phenyl ring. For compounds with no or only one *o*-substituent the compression effect is the dominant.

Steric interference

$^2\Delta\text{C-1 (ND)}$ vs. $^3\Delta\text{C-2' (ND)}$. The twist is much larger in **26** and **27** in which the two-bond isotope effects, $^2\Delta\text{C-1 (ND)}$ decrease, meaning that in this case the twist effect dominates. As seen from Fig. 4 a good correlation is found between $^3\Delta\text{C-2' (ND)}$ vs. $^2\Delta\text{C-1 (ND)}$ for compounds with a methyl group at C-1. For those compounds with no methyl substituent at C-1, the slope is much less. **14** is also seen to fall on this line. The negative or small effects at C-2', and C-6' are clearly related to the steric interference with the methyl group at C-1. Deuteriation at the NH position leads to a shorter NH bond on average, but also to a lengthening of the O...N distance.²¹ The latter effect is apparently the dominant. The negative effect can therefore be understood in terms of the chemical shift differences observed between C-2' of e.g. **1** and **10** or **15**. By deuteriation more of the twisted form is produced, which means that the chemical shift is shifted to higher frequency. A similar trend for $^5\Delta\text{C-4' (ND)}$ can be explained in the same fashion and lends support to the suggestion.

EXPERIMENTAL

Compounds

Compounds **1-7,9,12** and **13** were prepared by the procedure of Claisen,²² Rateb²³ and de Kimpe²⁴ stirring a water or ethanolic solution of equimolar amounts of the sodium salts of benzoylacetalddehyde and the hydrochloride of the appropriate amine at room temperature for 30 min to 1hr. Compounds **8,10,11,15** and **16** were synthesized according to Brown and Nonhebel.²⁵ An alcoholic solution of equimolar amounts of β -dicarbonyl compound and the appropriate amine was gently boiled on a water bath for 2hrs. **14** was obtained according to Roberts and Turner²⁶ and Grimshaw²⁷ refluxing a mixture of equimolar amounts of dibenzoylmethane and freshly distilled aniline in absence of a solvent until violent bumping. Compounds **15 - 28** were synthesized according to D.F. Martin *et al.*¹⁸ using acetylacetone and the appropriate amine and 2,6-dimethyl-3,5-heptanedione and *o*-fluoroaniline for **29**. The compounds were distilled and recrystallized before use. The yields were about 50% after distillation and recrystallisation. The melting points(in °C) and colours were: **1**, 139 (pale yellow); **2**, 207 (yellow); **3**, 265-266 (pale yellow); **4**, 171 (scarlet); **5**, 144 (yellow); **6**, 103 (yellow); **7**, 157 (yellow); **8**, 173 (yellow); **9**, 184-185 (yellow); **10**, 109-110 (pale yellow); **11**, 91-92 (yellow); **12**, 77-81 (cream); **13**, 136 (cream); **14**, 95.5-8 (yellow); **15**, 46 (white, colourless); **16**, 64-65 (light brown); **17**, 140.5-141.1 (yellow); **18** (red oil); **19** 78.5-79.8 (cream); **20** 77.9-79.1 (yellow); **21** (yellow oil); **22** 59.5-60.5 (cream); **23** (red oil); **24**, 49.4-49.7; **25**, (red oil); **26** (red oil); **27**, 45.2-45.6 . In those cases in which an oil was obtained too little compound was available for boiling point determination except for **29**, boiling point 268 °C. **30-32** were bought from Maybridge Chemical Company, Tintagel, UK and used without further purification. 2,6-dimethyl-3,5-heptanedione was synthesized according to Adams and Hauser.^{28,29} Acetylacetone was purchased from Aldrich, Weinheim, Germany and the fluoroanilines from Fluorochem, Glossop, UK.

NMR

The ¹³C NMR spectra of deuteriated species were recorded at 300 K in CDCl₃ or at 310 K in DMSO-d₆ on a Bruker AC 250 NMR spectrometer at 62.896 MHz with a digital resolution of 0.55 Hz per point. Chemical shifts are measured relative to internal TMS. Spectra of both deuteriated and non-deuteriated species, and of mixtures of the two species

were recorded for all compounds.

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Legends

Scheme 1

Deuterium isotope effects on ^{13}C chemical shifts.^{a,b}

- ^a Compounds are dissolved in DMSO- d_6 . Values are given in ppm.
- ^b The NH and OH chemical shifts are given in italics. The deuterium isotope effects are given in the order $^n\Delta\text{C}(\text{ND})$, $^n\Delta\text{C}(\text{D})$. For **5** and **9** the order is $^n\Delta\text{C}(\text{ND})$, $^n\Delta\text{C}(\text{OD})$.
- ^c Numbers in brackets are obtained from CDCl_3 .
- ^d The \underline{g} -form is not observed in DMSO- d_6 .
- ^e Isotope effects are not observed. br means broad.
- ^f May be interchanged
- ^g Only large isotope effects are observed
- ^h This isomer is not very abundant
- ⁱ At 250 K
- ^j At 230 K
- ^k $^3\text{J}(\text{H},\text{H})$ in Hz.

Fig. 1

Numberings of the enamminones

Fig. 2

Resonance forms of enamminones.

Fig. 3

Plot of $^2\Delta\text{C}-1(\text{ND})$ vs. δNH .

Legends: R_1 , R_2 and R_3 (see Fig. 1). CH_3 , CH_3 , Ph; Ph, Ph, Ph; Ph, CH_3 , Ph; Ph, H, Ph; alkyl, CH_3 , alkyl. Data taken from Ref. 3; alkyl, H, Ph. Data taken from Ref. 3; Ph, H, alkyl.

Fig. 4

Plot of $^2\Delta\text{C-1(ND)}$ vs. $^3\Delta\text{C-2'(ND)}$.

Legends: H at C-1. Solvent DMSO- d_6 ; H at C-1. Solvent, CDCl_3 ; CH_3 at C-1. Solvent, CDCl_3 .

Data for compounds **22** - **24** and **29**, compounds with halogens in *o*-position are not included.

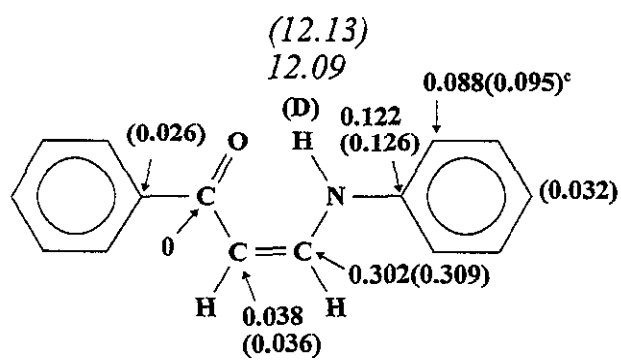
Footnotes to Table 1

- ^a Numbering in this table is as shown in Fig. 1, irrespective of correct IUPAC numbering in order to make comparisons easier.
- ^b Benzyl ring is numbered as ring A
- ^c Measured in CDCl_3 . Compound **32** is 100% E isomer.
- ^d May be interchanged
- ^e Broad resonance
- ^f Not resolved
- ^g $J(\text{C},\text{F})$ in Hz.
- ^h Resonance not observed. May be obscured by signal from Z-isomer.

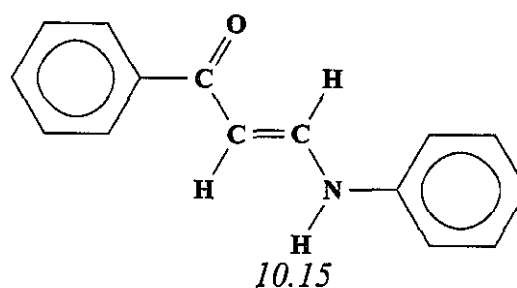
Table 1. ¹³C chemical shifts (ppm).

	C-1	C-2	C-3	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	C-1''	C-2''	C-3''	C-4''	(
1Z ^c	144.69	93.53	190.74	140.01	116.11	129.52	123.46	129.52	116.11	139.00	128.22	127.11	131.34	1
1Z	145.97	93.66	189.62	140.17	116.40	129.81	123.57	129.81	116.40	138.81	128.70	127.27	131.83	1
1E	144.57	97.66	187.57	141.14	115.82	129.81	122.56	129.81	115.82	139.67	128.62	127.35	131.59	1
2Z	144.71	93.27	189.19	128.41	145.99	115.62	123.71	120.06	113.92	139.14	128.68	127.25	131.65	1
2E	144.44	~98	~187.65	h	~145	115.83	123.44	h	h	139.96	128.60	127.38	131.47	1
3Z	144.95	94.97	190.26	143.44	115.91	131.38	125.29	131.38	115.91	138.59	128.82	127.48	131.96	1
3E	145.16	99.78	187.94	144.10	115.05	131.53	124.14	131.53	115.05	139.36	128.76	127.55	131.21	1
4Z	146.47	91.81	188.60	129.93	117.76	113.74	151.73	113.74	117.76	139.25	128.69	127.10	131.49	1
4E	147.77	-	h	h	117.84	133.89	151.76	113.89	117.84	139.23	128.58	127.24	131.31	1
5Z ^c	145.49	92.23	193.96	139.74	116.45	129.68	124.08	129.68	116.45	128.14	162.49	118.31	134.17	1
5Z	147.30 ^d	92.56	193.03	139.90	116.94	129.86 ^d	124.18	129.86 ^d	116.94	128.99	161.76 ^d	120.19	134.79	1
5E	146.35 ^d	95.69 ^c	191.76	140.57	116.33 ^c	129.78 ^d	123.39	129.78 ^d	116.33 ^c	128.68	162.43 ^d	118.95	134.74	1
6Z ^c	143.55	98.68	191.57	140.18	116.00	129.43	123.18	129.43	116.00	129.73	157.38	111.38	131.72	1
6Z	144.52	98.94	190.71	141.26	116.31	129.87	123.42	129.87	116.31	129.66 ^d	157.48 ^d	112.36 ^d	132.40	1
6E	144.00	103.87	189.99	140.39	115.58	129.84	122.40	129.84	115.58	129.32 ^d	157.08 ^d	112.20 ^d	131.55	1
7Z	145.26	93.21	186.34	141.32 ^d	116.22 ^d	129.87 ^d	123.35	129.87 ^d	116.22 ^d	131.55	129.43 ^d	114.00	162.18	1
7E	143.85	97.39	188.83	140.36 ^d	115.69 ^d	129.86 ^d	122.38	129.86 ^d	115.69 ^d	132.33	129.47 ^d	113.89	162.36	1
8Z	147.58	93.58	187.16	139.81	116.90	129.86	124.21	129.86	116.90	144.00	128.58	123.90	149.20	1
8E	149.26	97.67 ^c	185.89	140.72	116.21 ^c	129.84	123.17	129.84	116.21 ^c	145.04	128.64	123.88	149.03	1
9Z	146.11	92.39	192.78	127.92	146.24	115.80	124.54	120.30	114.33	128.89	161.91	118.04	134.70	1
9E	147.63 ^c	~97 ^c	191.80	128.46 ^c	147.60 ^c	116.06	~124.5 ^c	120.33	h	128.66	162.66	h	h	h
10Z ^c	162.05	94.13	188.56	138.54	124.66	129.03	125.64	129.03	124.66	139.91	128.14	126.93	130.75	1
10Z	162.42	93.99	187.23	138.34	124.14	129.37	125.58	129.37	124.14	139.50	128.43	126.93	131.11	1
11Z ^c	162.40	93.74	188.31	135.86	124.67	129.58	135.53	129.58	124.67	139.98	128.09	126.88	130.62	1
11Z	162.70	93.62	189.01	135.71	124.21	129.83	135.05	129.83	124.21	139.59	128.41	126.88	131.02	1
12Z ^c	153.87	90.68	190.01	137.59	128.67	127.61	127.08	127.61	128.67	139.50	128.08	126.94	130.80	1
13Z ^c	155.35	90.15	189.85	35.24	-	-	-	-	-	139.73	128.04	126.89	130.69	1
13Z	156.11	89.13	187.61	35.05	-	-	-	-	-	139.73	128.20	126.72	130.71	1
14Z ^c	161.37	96.93	189.57	139.37	123.09	129.56	124.00	129.56	123.09	135.75	128.25	127.15	131.17	1
14Z	161.11	96.76	188.68	139.26	123.08	128.94	124.28	128.94	123.08	135.26	128.56	127.25	131.64	1
15Z ^c	160.01	97.43	195.93	138.59	124.56	128.90	125.36	128.90	124.56	28.97	-	-	-	-
15Z	159.73	97.63	195.08	138.48	123.93	129.29	125.23	129.29	123.93	28.96	-	-	-	-
16Z ^c	159.49	97.96	196.36	137.26	125.70	129.05	130.85	129.05	125.70	29.05	-	-	-	-
16Z	160.13	98.53	196.19	137.75	125.93	129.58	129.85	129.58	125.93	29.31	-	-	-	-
17Z ^c	157.03	101.22	197.90	145.37	121.92	125.21	143.56	125.21	121.92	29.63	-	-	-	-
18Z ^c	161.69	96.24	195.18	127.63	126.31	112.48	148.79	112.48	126.31	28.89	-	-	-	-
19Z ^c	158.50	99.43	196.98	143.21	122.71	130.76	131.39	130.76	122.71	29.41	-	-	-	-

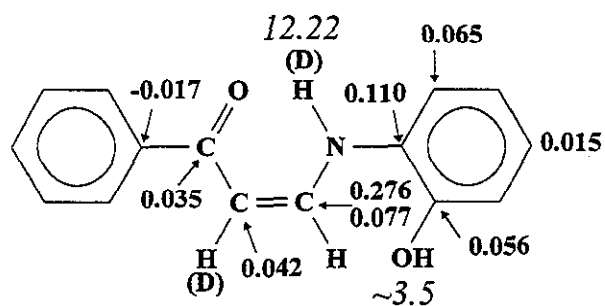
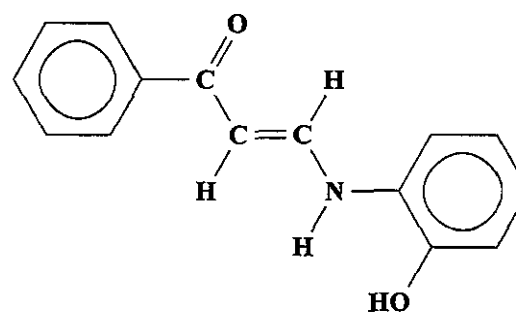
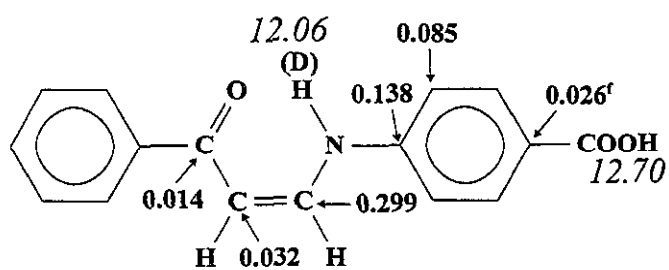
20Z ^c	158.21	99.77	197.13	143.54	122.57	129.71	133.19	129.71	122.57	29.46	-	-	-	20.40	C=O; 196.70, CH ₃ ; 26.44
21Z ^c	160.82	96.76	195.66	137.19	133.34	130.47	126.08	126.08	125.91	28.74	-	-	-	19.27	Ar-CH ₃ ; 17.73
22Z ^c	159.37	98.20	196.44	136.10	129.53	129.83	126.50	126.50	126.89	28.98	-	-	-	19.48	
23Z ^c	159.47	98.08	196.58	137.67	N.R.	N.R.	N.R.	N.R.	N.R.	29.10	-	-	-	19.57	
24Z ^c	160.16	97.92	196.41	126.62	156.37	115.97	126.93	126.81	124.05	28.92	-	-	-	19.20	
				12.45 ^g	247.5 ^g	20.19 ^g	7.61 ^g	0.88 ^g	4.34 ^g					2.45 ^g	
25Z ^c	160.09	97.95	196.43	138.60	128.52	131.53	112.52 ^d	160.90	112.48 ^d	29.03	-	-	-	19.58	Ar-CH ₃ ; 17.30
				9.75 ^g	3.2 ^g	4.91 ^g	22.96 ^g	243.97 ^g	21.07 ^g						
26Z ^c	161.48	96.78	195.63	136.53	142.77	126.57	127.09	149.41	123.63	28.95	-	-	-	19.77	C(CH ₃) ₃ -2/6; 34.55/34.10, CH ₃ -2/6; 31.13/30.55
27Z ^c	162.42	95.50	195.62	136.27	135.80	127.90	127.12	127.90	135.80	28.74	-	-	-	18.52	Ar-CH ₃ ; 17.91
28Z ^c	159.25	98.43	196.64	140.22	127.29	122.43	128.22	130.20	122.96	29.19	-	-	-	19.79	
29Z ^c	171.66	90.70	203.80	126.27	156.95	115.97	127.32	127.92	124.11	39.83	21.56	-	-	28.71	CH ₃ -2'''; 19.45
				12.70 ^g	247.24 ^g	20.82 ^g	7.61 ^g	0.82 ^g	3.40 ^g					1.89 ^g	
30Z ^c	155.05	89.60	190.06	-	-	-	-	-	-	119.96	158.79	118.90	120.82	-	N(CH ₃) ₃ ; 37.27, 45.28
										5.98 ^g	1.64 ^g	7.23 ^g	23.40 ^g	23.59 ^g	
31Z ^c	155.55	89.47	189.42	-	-	-	-	-	-	121.19	147.93	151.29	108.04	-	N(CH ₃) ₃ ; 37.35, 45.41
										4.40 ^g	12.64 ^g	248.47 ^g	238.19 ^g	22.83 ^g	
										7.42 ^g	2.71 ^g	11.48 ^g	27.20 ^g	3.96 ^g	
32Z ^c	146.02	117.57	192.60	127.95	117.28	146.54	143.78	117.83	122.99	119.58	159.60	119.67	123.53	114.35	O-CH ₂ -CH ₂ -O; 64.09, 64.56
											1.32 ^g	7.17 ^g	23.77 ^g	23.52 ^g	



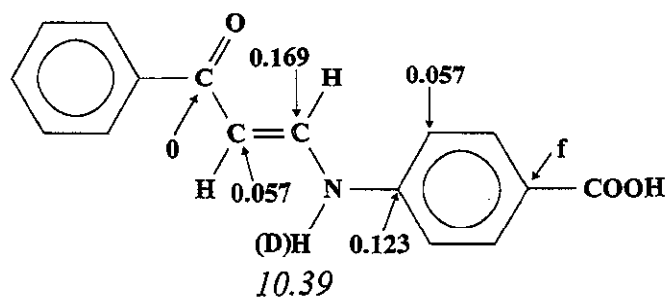
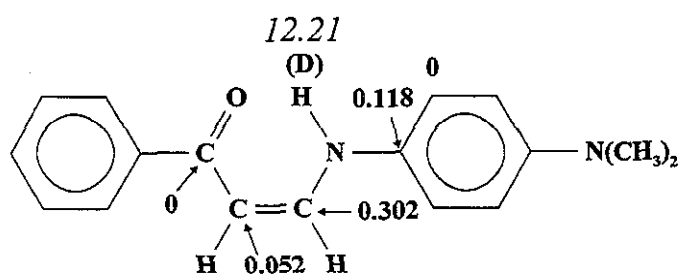
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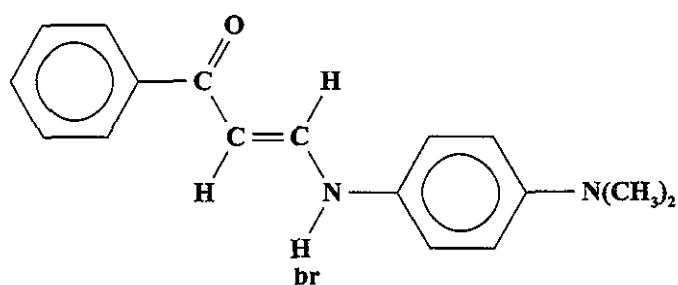
1E^e

 $2Z^d$  $2E^d$ 

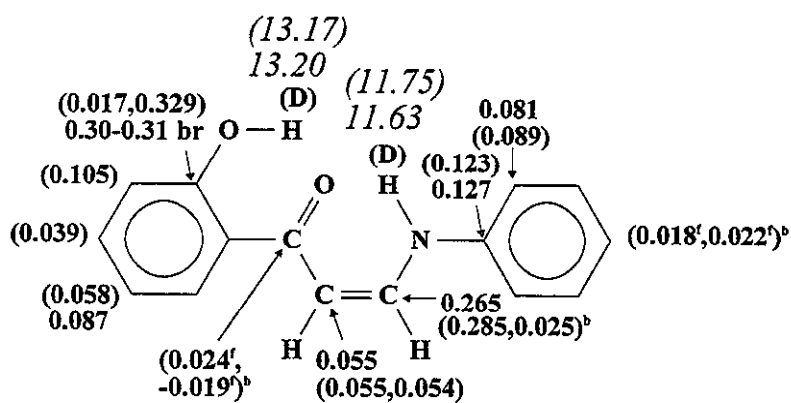
3Z

**3E**

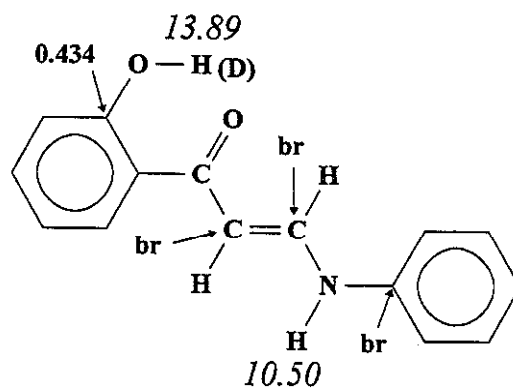
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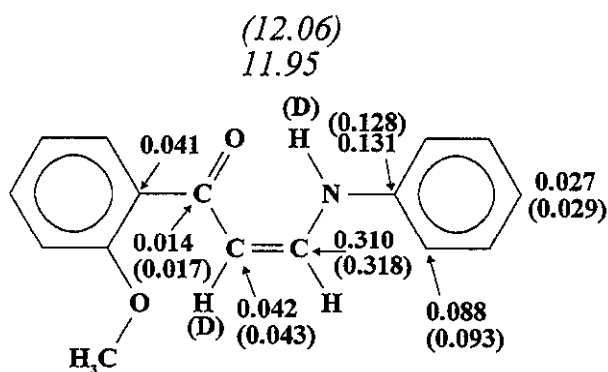
4E^e



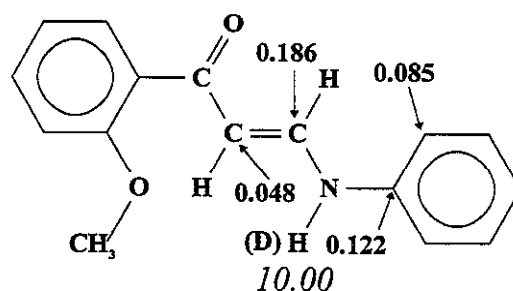
5Z



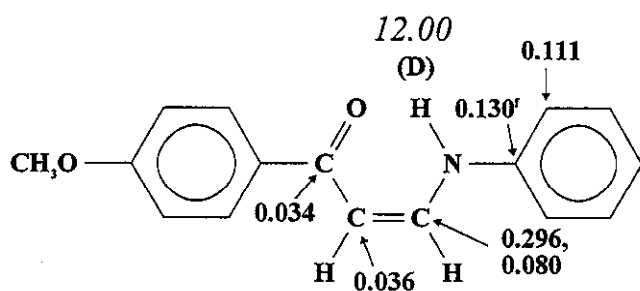
5E^g



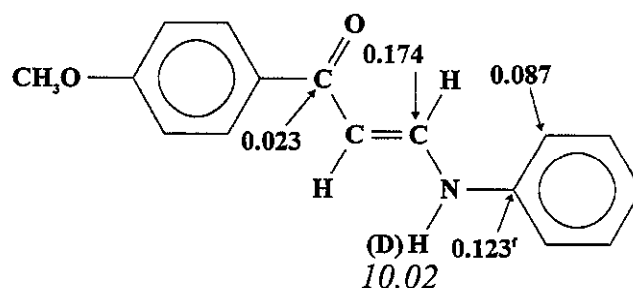
6Z



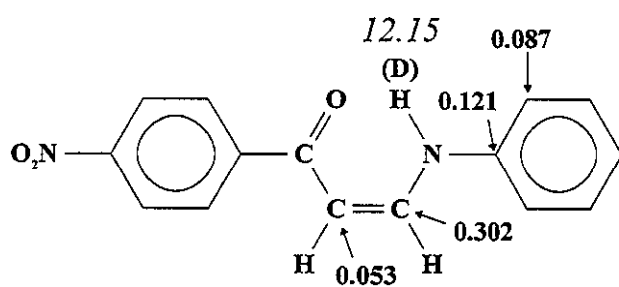
6E



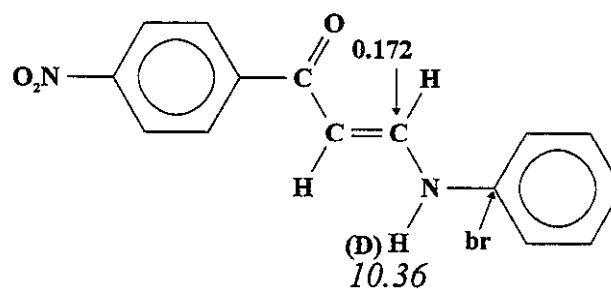
7Z



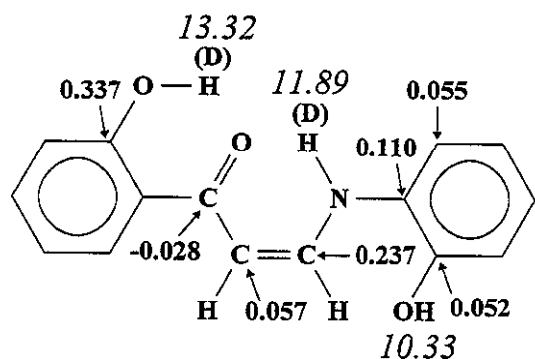
7E



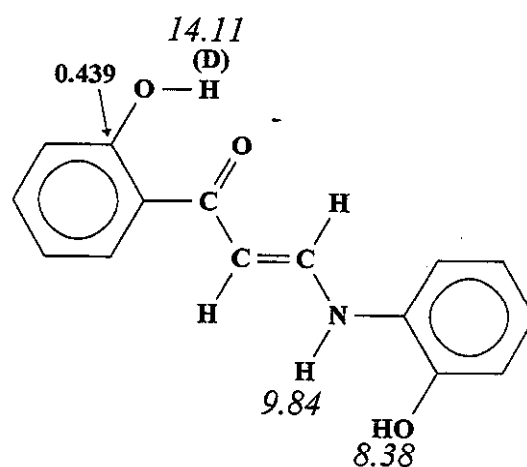
8Z



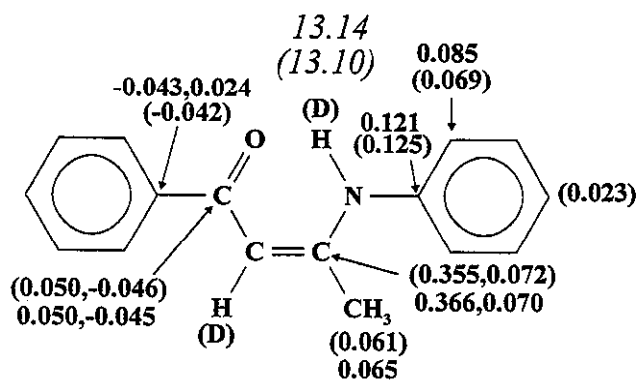
8E



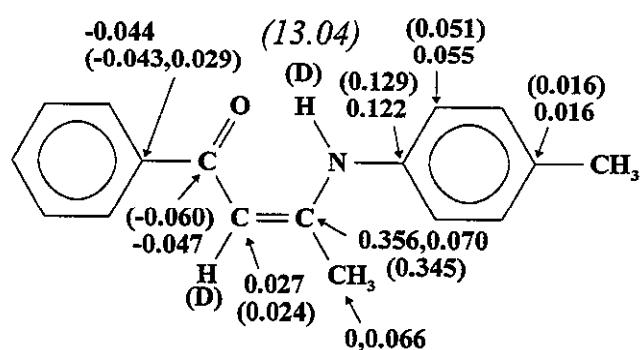
9Z



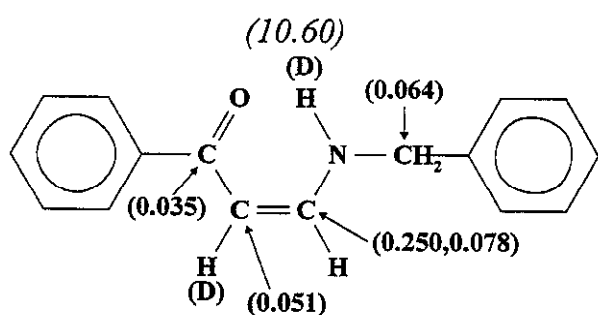
9E^h



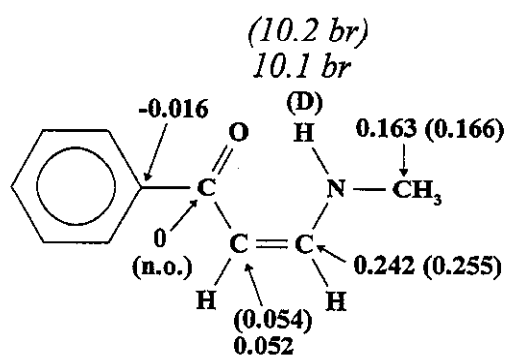
10Z



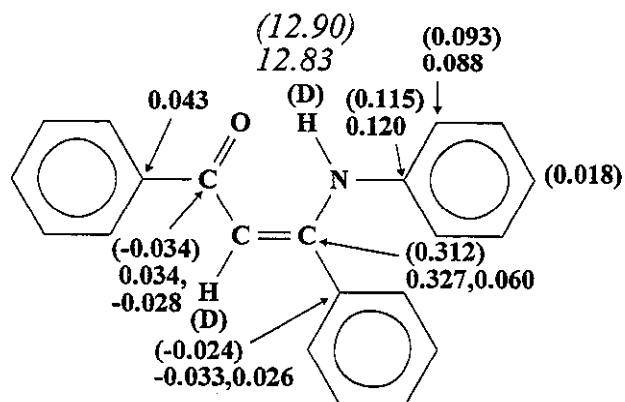
11Z



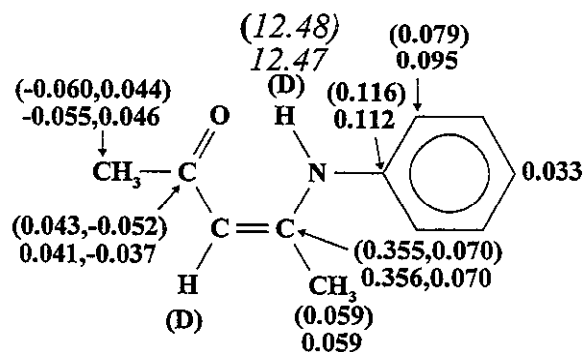
12Z



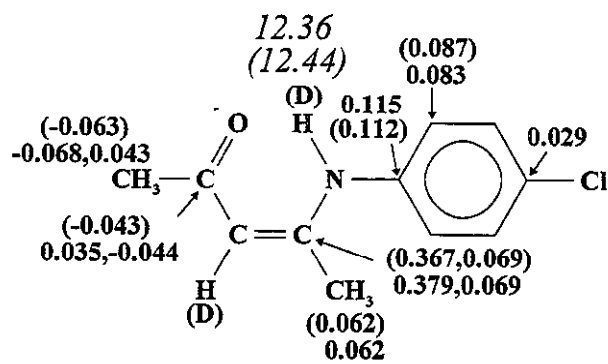
13Z



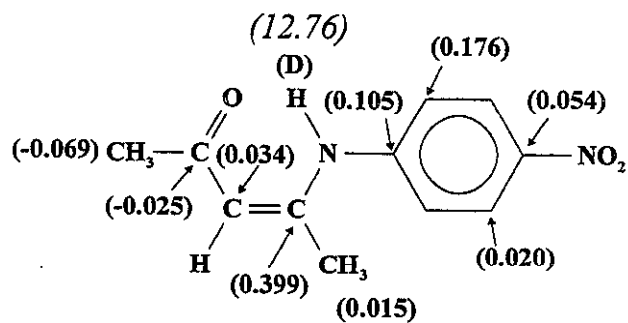
14Z^d



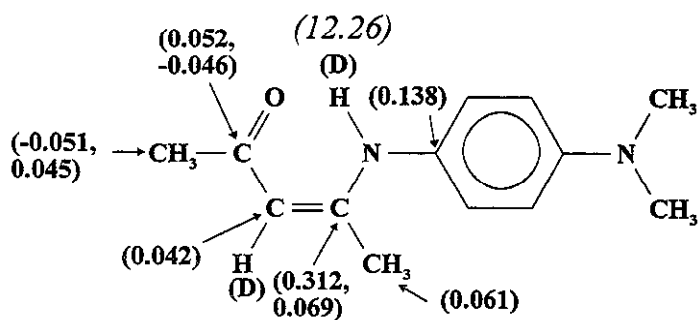
15Z^d



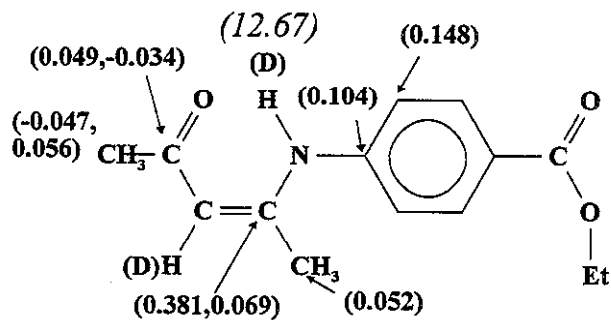
16Z



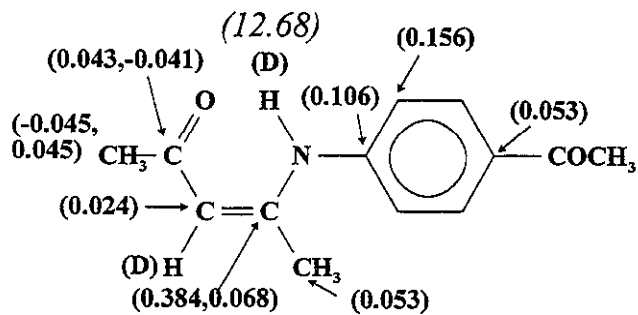
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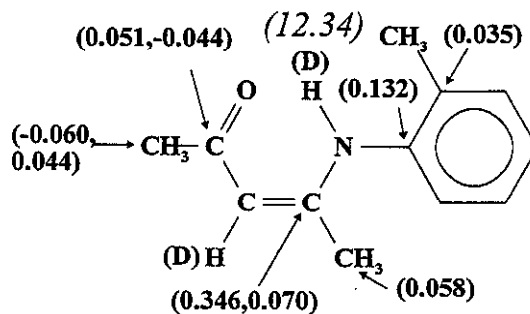
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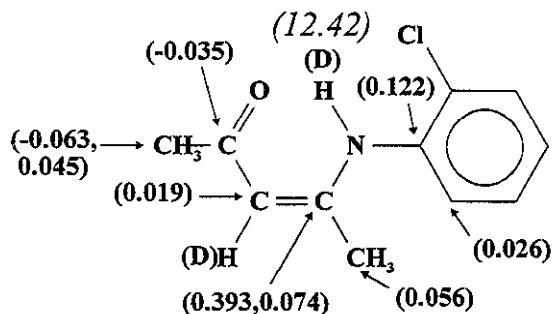
19Z



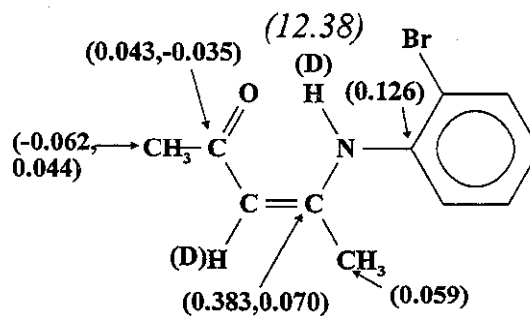
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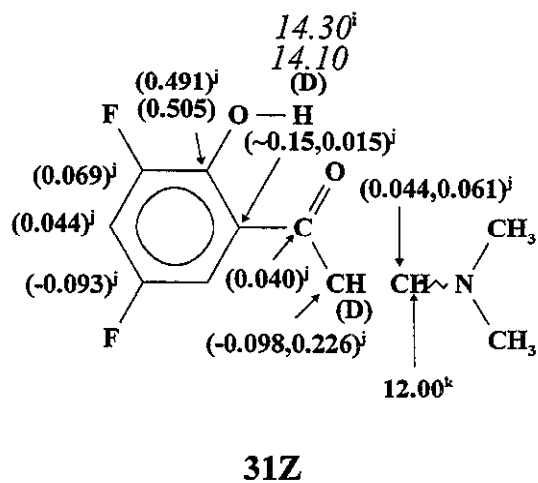
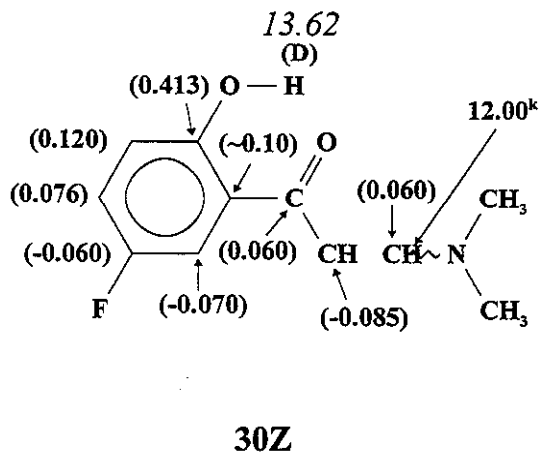
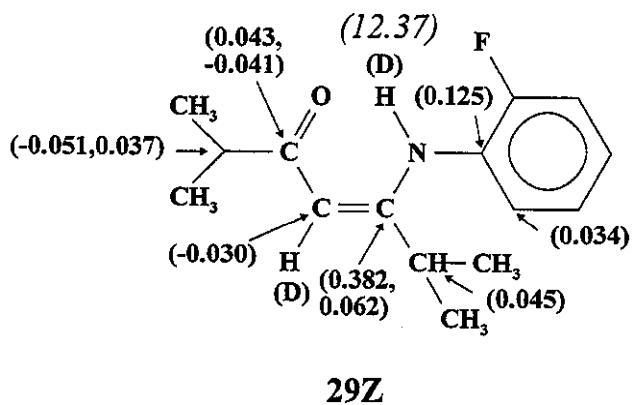
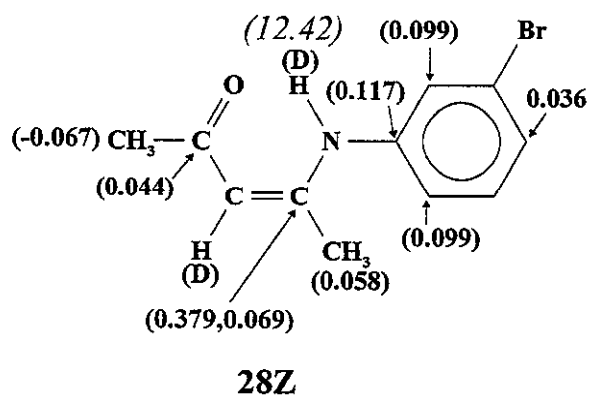
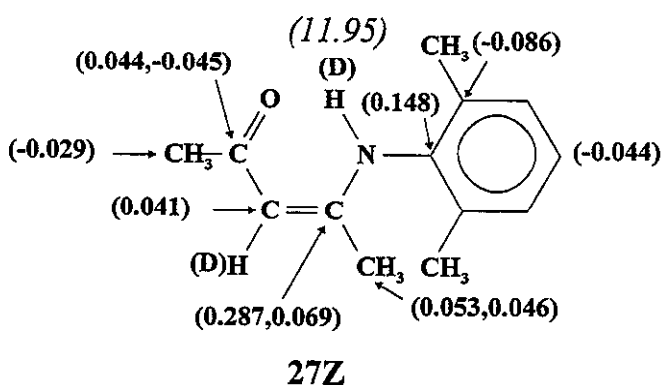
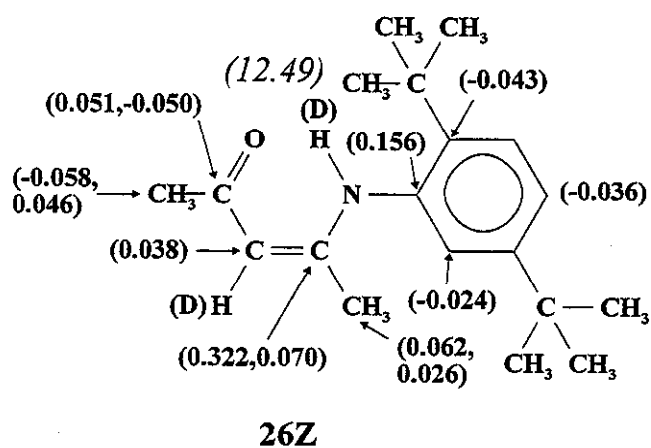
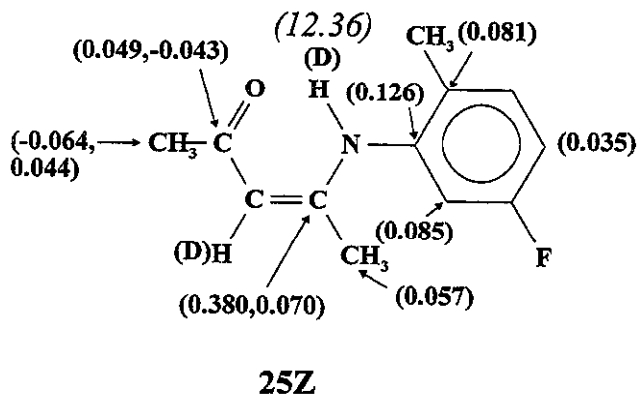
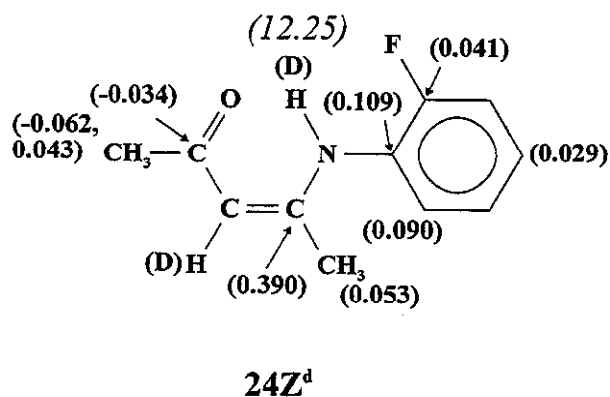
21Z



22Z



23Z





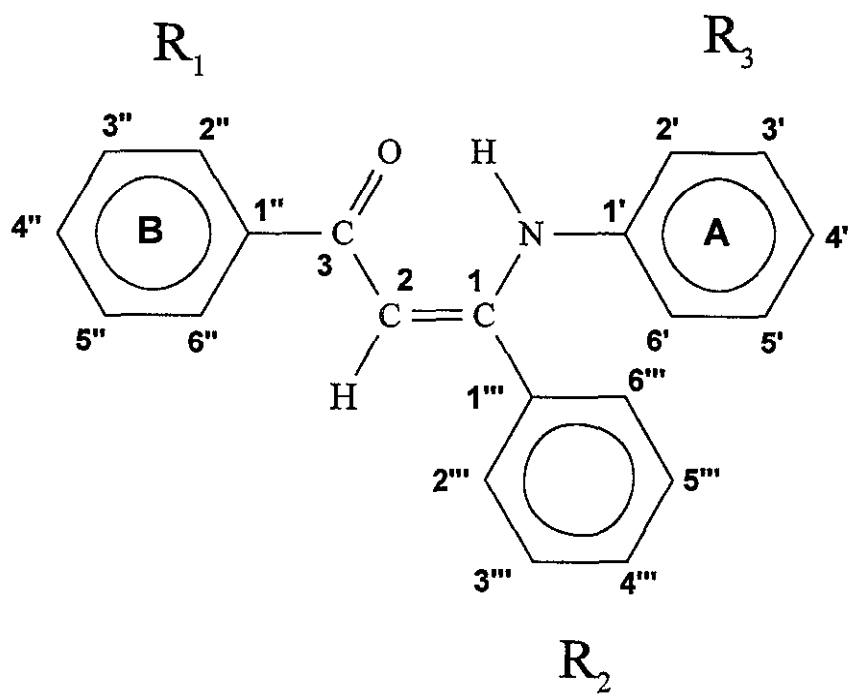


Fig. 1

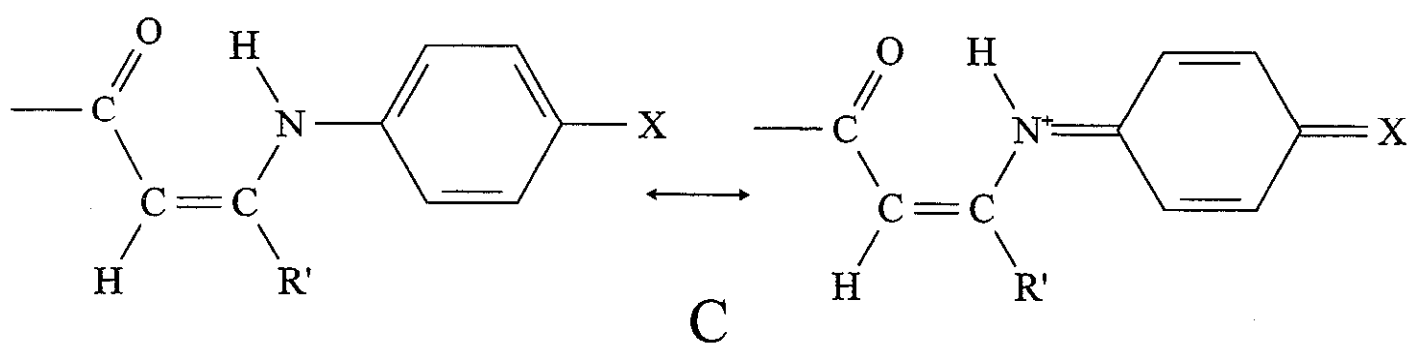
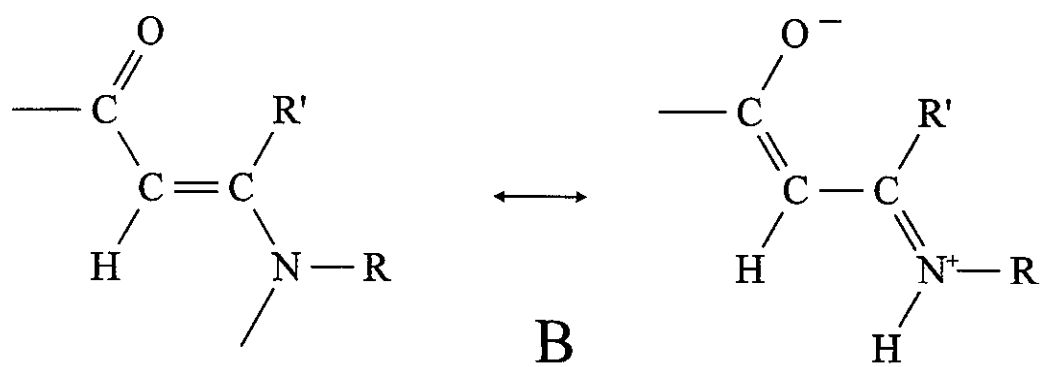
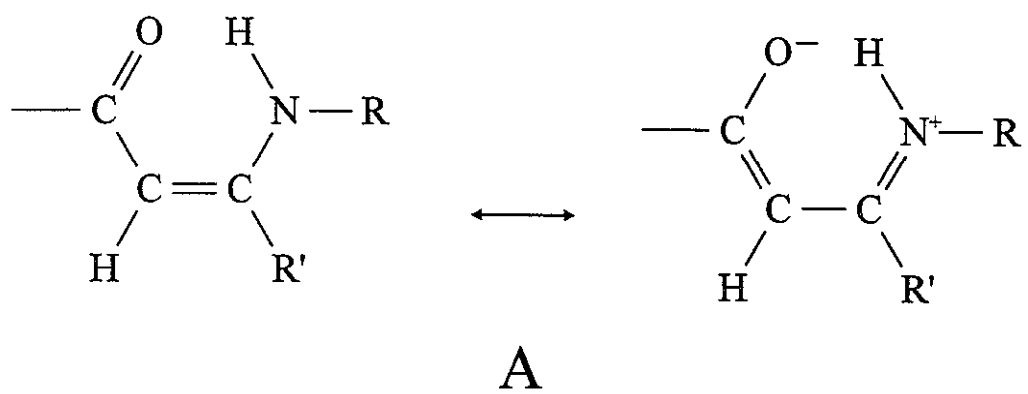


Fig. 2

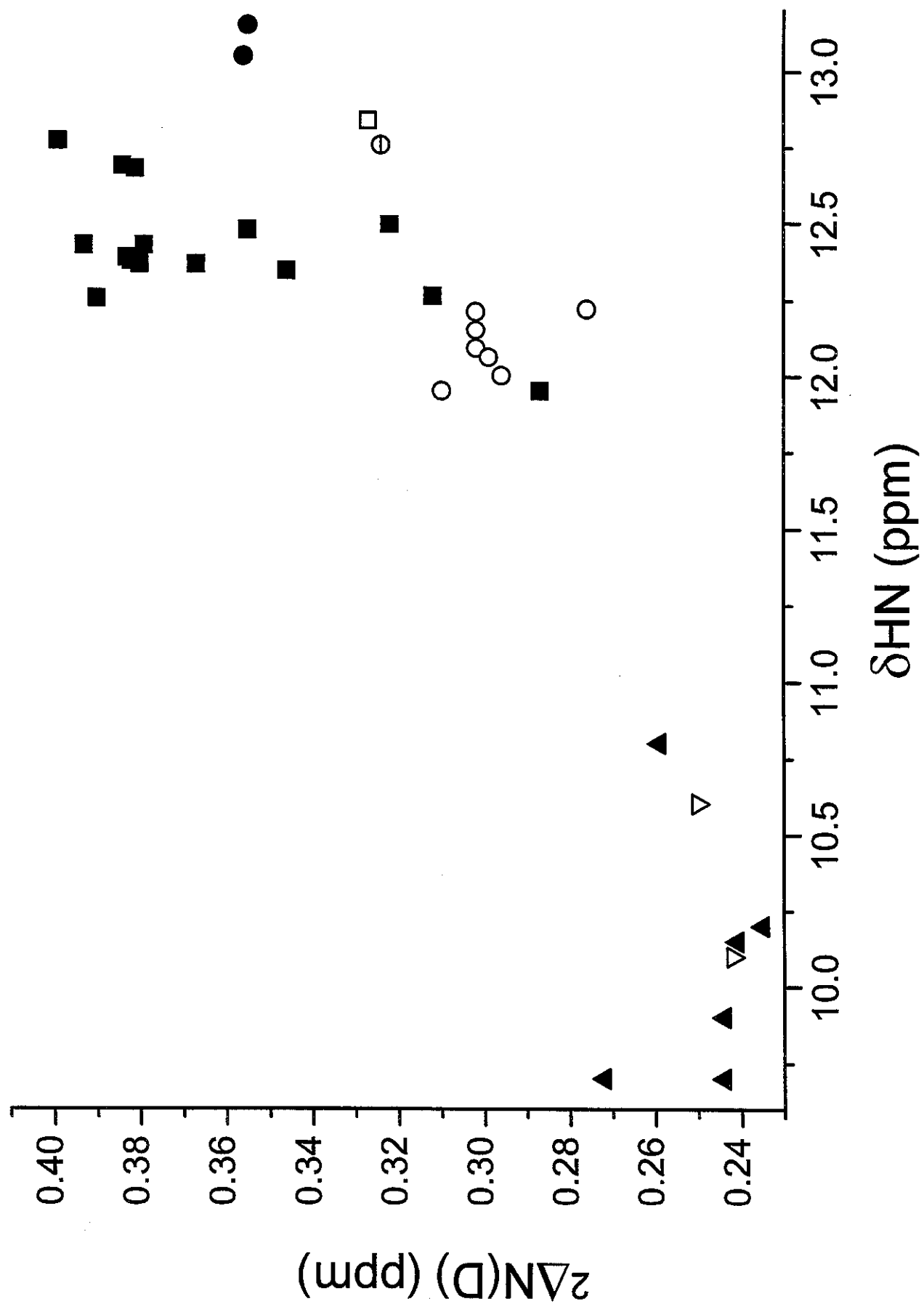


Fig. 3

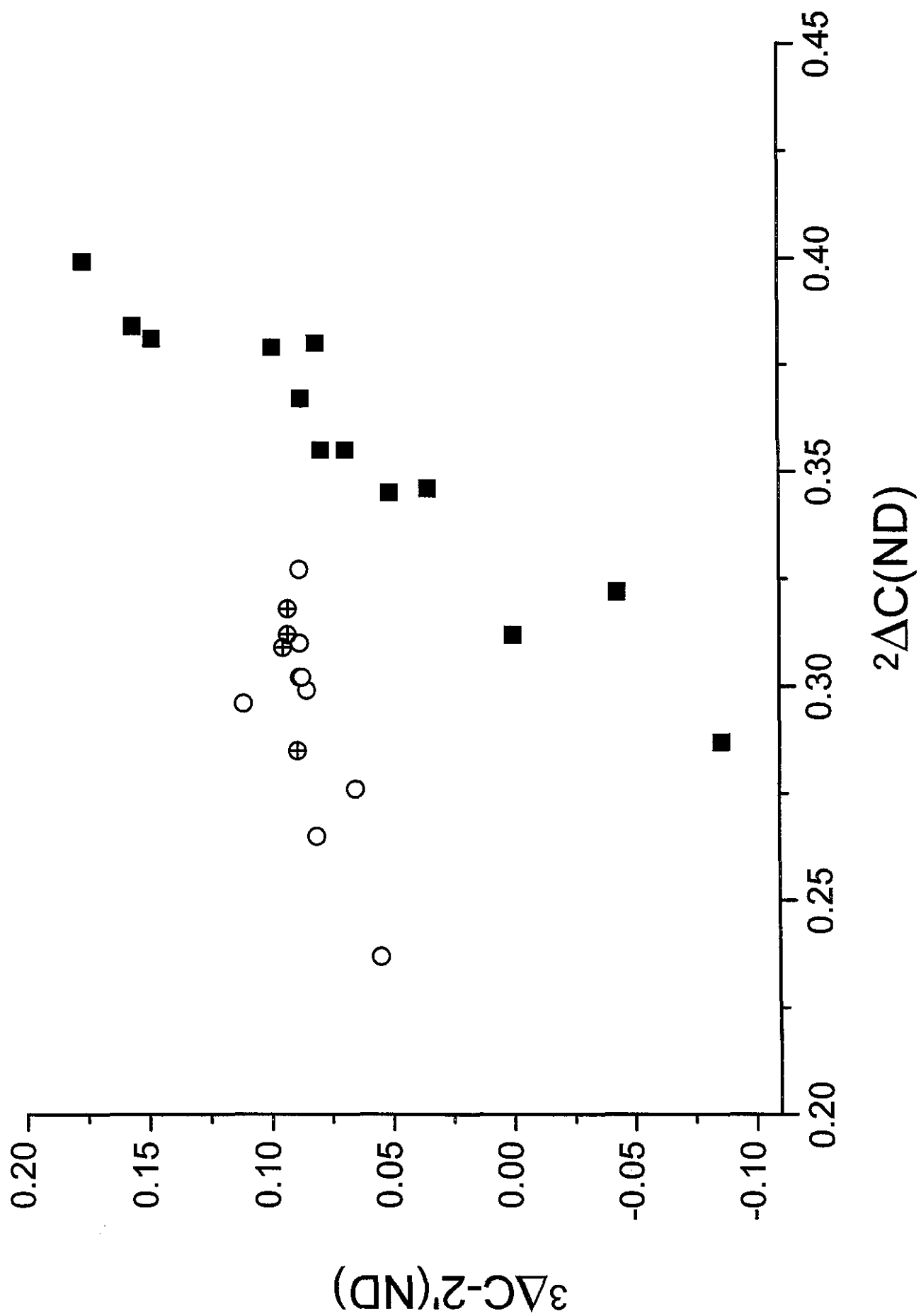


Fig. 4

Paper VIII

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Roskilde University , P.O.Box 260, DK-4000 Roskilde, Denmark

Running title: Long range deuterium Isotope Effects on ^{19}F Chemical Shifts.

Long Range Intrinsic and Equilibrium Deuterium Isotope Effects on ^{19}F Chemical Shifts.

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ABSTRACT

Deuterium isotope effects on ^{19}F chemical shifts caused by deuteriation at OH or NH groups are determined in intramolecularly hydrogen bonded compounds containing fluorinated *o*-hydroxyacyl aromatics, enaminones, *o*-hydroxyazo and hydrazo compounds. The latter represent both tautomeric and non-tautomeric cases. Deuterium isotope effects on fluorine chemical shifts are found for *o*-hydroxyacyl aromatics to be parallel to deuterium isotope effects at the carbon ipso to fluorine. For the azo and hydrazo compounds very long-range effects are seen formally over ten bonds. Through-space effects are observed in case of spatially close nuclei like 2-fluorobenzamide-ND.

The isotope effects on ^{19}F chemical shifts can in *para*-fluorophenyl substituted cases be used to monitor the change in equilibrium upon deuteriation and therefore to estimate the importance of hydrogen bonds.

INTRODUCTION

Deuterium isotope effects on ^{19}F chemical shifts have been investigated in carbenium ions,^{1,4} acylfluorides,⁵ fluoroethylenes⁶ and fluorobenzenes.⁷ Long-range deuterium isotope effects on fluorine chemical shifts have been studied in bicyclo compounds in order to elucidate the mechanism.⁸ In the latter compounds with large distances between deuterium and fluorine, it was found that the effect is mediated through the σ -electron skeleton. ^{19}F is a very sensitive nucleus both regarding detection and chemical shifts. Therefore, ^{19}F chemical shifts have been used with success to monitor tautomeric equilibria.^{9,10}

Solvent deuterium isotope effects on ^{19}F chemical shifts have also proven very useful.^{11,12} In that context compounds with exchangeable OH or NH groups next to fluorine were investigated.¹² It is interesting to compare isotope effects due to intramolecular hydrogen bonds and solvent isotope effects. Recently, 2-fluorobenzamide has been examined and a rather large "through-space" isotope effect was established caused by deuterium substitution at the nearby amide group¹³ and hence of orbital overlap type. As outlined above, a number of different mechanisms possibly depending on distance but also on hydrogen bonding exist. An elucidation of these intrinsic isotope effects is furthermore important as the intrinsic contribution must be known in order to use deuterium isotope effects as a gauge of equilibrium situations.

Deuterium isotope effects on chemical shifts are defined as ${}^n\Delta X(\text{D}) = \delta X(\text{H}) - \delta X(\text{D})$, where X is the observed nucleus, D is the heavier isotope (in this case deuterium) and n is the number of intervening bonds between the nuclei in question and the isotope.

Deuterium isotope effects on ^{13}C chemical shifts have been studied in a large number of intramolecularly hydrogen-bonded cases and this type of isotope effects show systematic trends.¹⁴⁻²⁰ In conjugated systems they are transmitted over many bonds²⁰ and the mechanism has been discussed.²¹ The charge separation in hydrogen bonded systems is of great interest.²² ^{19}F chemical shifts are very sensitive to electric field effects.^{23,24} It is clearly of interest to compare the isotope effects on carbon, ${}^n\Delta C(\text{XD})$, to isotope effects on ^{19}F chemical shifts, ${}^{n+1}\Delta F(\text{D})$, in the same compounds. A correlation between these parameters may be very useful in determining one when the other is known, but also in order to understand the mechanism better.

Equilibrium isotope effects have also been studied in detail^{25,26} and Bordner et al.²⁷

have raised the question of the functional form of the change in the equilibrium constant as a consequence of deuteriation. They suggested the unusual functional form $K^D = K^{1+\alpha}$ in which K^D is the equilibrium constant for the deuteriated compound. This has been confirmed in β -diketones²⁸ and in β -thioxoketones.²⁹ The fluorinated *o*-hydroxyazo compounds provide a very good test set as the three monofluorinated compounds have equilibrium constants between one and three at 300 K.

The present investigation covers deuterium isotope effects on ^{19}F chemical shifts of fluorinated *o*-hydroxyacyl aromatics, acetanilides, amides, enaminones, *o*-hydroxy-azo and hydrazo compounds. The latter compounds represent both tautomeric and non-tautomeric cases, some of which serve as models for estimation of standard values for the azo- and hydrazo cases.

RESULTS and DISCUSSION

XH chemical shifts, deuterium isotope effects on ^{19}F and ^{13}C chemical shifts are given in Scheme 1. ^{13}C chemical shifts and $J(\text{C},\text{F})$ coupling constants are given in Table 1 and the ^{19}F chemical shifts are given in Table 2.

Deuterium isotope effects on fluorine chemical shifts, $^n\Delta\text{F}(\text{XD})$.

o-Hydroxy acyl aromatics The deuterium isotope effects on ^{19}F chemical shifts over four bonds are positive for 2 and 6 and zero for 5. The isotope effects over six bonds, $^6\Delta\text{F}-5(\text{OD})$ are negative, whereas the effects over five bonds, $^5\Delta\text{F}-5(\text{OD})$, are small except for 8. A comparison of $^{n+1}\Delta\text{F}(\text{OD})$ with $^n\Delta\text{C}(\text{OD})$ for 1-7,9,10 revealed that the signs and also the magnitudes of the two types of isotope effects are very similar. The only exception is $^4\Delta\text{F}-3(\text{OD})$ of 5, which is zero. The parallel behaviour underlines either that the fluorine chemical shift depends on the perturbation in a manner different from that of ^{13}C or that an alternation in the effect,^{17,30} as suggested for the ^{13}C isotope effects, does not occur. An explanation for the non-alternation is possibly the transmission of $^4\Delta\text{F}(\text{D})$ through the σ -electron skeleton.

The value observed for 8 is clearly unusual. This is most likely related to strain isotope effects expected for such systems.³¹

Compounds with NH-Ph fragment. These compounds are divided into two groups, those having the NH group taking part in intramolecular hydrogen bonding, 11-13,16-21 and those not, 26-28. 18 and 19 have in addition a non-hydrogen bonded NH group far from the fluorine. The $^4\Delta F-2'(ND)$ isotope effects are rather similar in the localized hydrogen bonded cases except for 13 and all the values are close to 0.060 ppm. This is only half the size of the isotope effect observed for the tautomeric compound, 25. The lack of $^5\Delta C(ND)$ isotope effects of the acetanilide and hydrazones can be ascribed to the lack of hydrogen bonds of the RAHB type in the former. In that light it is unusual that $^6\Delta F(D)$ of 19,21,28 and to a certain extent 31 are large and positive. This suggests a different origin of the isotope effect. The relatively large value of $^n\Delta F(D)$ for the *o*-fluoro compounds, 26 and 29, compared to the *m*- and *p*-fluoro compounds, 27,28, 30 and 31 can possibly be seen as a consequence of close proximity of the NH(D) and the fluorine in the *o*-fluoro compounds.³² That proximity plays a role for this kind of isotope effects has been demonstrated for 29. In this case the isotope effect on the fluorine chemical shift for the proximate ND is 0.138 ppm, whereas it is only 0.016 ppm for the ND pointing away from the fluorine.¹³ Furthermore, the close proximity of NH and F in 29 is assured through observation of large through space H-F coupling.³² It is also noticeable that 27 does not show an isotope effect. The effect of proximity has also been claimed as the cause of a large $^3\Delta F(D)$ effect of fluorobenzene-2-*d*.⁷

As mentioned above $^4\Delta F(D)$ of 13 is much smaller than for 11. The same is found for $^3\Delta C-2(ND)$ and $^3\Delta C-6(ND)$. This is not the case for neither $^2\Delta C-1(ND)$ or $^2\Delta C-1'(ND)$, although this had been suspected.³³

D₂O:H₂O solvent isotope effect on fluorine of 29 are actually larger (0.199 ppm),¹² than that observed in CDCl₃ (0.138 ppm). This is in line with the previous conclusion, that the intramolecular contribution in H₂O:D₂O is small.¹²

Extraordinary long range isotope effects on fluorine formally over eight bonds are seen from the amide like NH group of 18. A similar, but smaller effect was seen for 19 in which the distance is longer.

Azo compounds The isotope effect for 15 is exceptional. If it is transmitted through bonds, the pathway is over ten bonds. Another transmission pathway would be via the hydrogen bond. Similar effects are in principle seen for $^n\Delta C(XD)$, but not to the same extent. The

small isotope effects in general, assures that no tautomeric equilibrium is at play (see later), so that 14 and 15 can be used as models for azo compounds. The value for 14 is larger than that for 15 in good agreement with the smaller number of bonds.

General effects

¹⁹F chemical shifts The ¹⁹F chemical shifts of the *o*-acyl aromatics are falling in three different ranges, F-3 substituted at ~ -135 ppm, F-5 substituted at ~ -117 ppm and F-6 substituted at ~ -105 ppm with compound 8 again falling outside at -100.2 ppm.

For the NH compounds F-2 substituted fall at ~ -132 ppm with the values of the enaminones at ~ -123 ppm. For F-4 substitution, the values are ~ -117 ppm (Table 2). The value mentioned for the NH compounds including hydrazo compounds are different from those found for azo compounds. F-2 substituted are at -125.1 ppm and F-4 substituted at -109.5 ppm according to the model compounds, 14 and 15 (Table 2). The values for the azo compounds are known to be influenced by substituents.³⁴ The values found for hydrazo compounds confirm those found by Lycka^{9,10} and therefore make possible the use of ¹⁹F chemical shifts to estimate the amounts of hydrazo and azo forms of hydrazo-azo tautomeric equilibria⁹ (see later).

It has been demonstrated, that in certain cases the ⁿΔX(D) simply reflect the chemical shift of X.²¹ A proportionality was found between ⁷ΔF(D) and δF of deuteriated 4-fluorophenylethyl carbonium ions.⁴ No such trend is seen for 1, 2, 31, 17 and 21 (Scheme 1).

¹J(C,F). For fluorinated compounds, ¹J(C,F), (Table 1) couplings tell about the double bond character of the C-F bond^{35,36} and followingly about the fluorine lone-pair delocalization. The ¹J(C,F) couplings are seen to vary in 1-10 according to the fluorine position so the ¹J(C-6,F) > ¹J(C-4,F) > ¹J(C-3,F) > ¹J(C-5,F). For the NH compounds the variation in ¹J(C,F) is much smaller and a nearly constant value is found for both *o*- and *p*-fluorinated compounds. For the *ortho*-case a larger coupling is found for the azo than for the hydrazo case. The ¹J(C,F) couplings are therefore a possible way of determining the position of azo-hydrazo tautomeric equilibria (see later).

Tautomeric equilibria. The determination of equilibrium constants in the tautomeric

compounds can be based on chemical shifts of nuclei sensitive to the difference between the azo and hydrazo forms. The nuclei should at the same time be isolated from local changes in the structure. Lycka et al.³⁷ have tested the use of C-1', C-2' and C-4' of phenyl rings and for fluorine substituted compounds, $\delta^{19}\text{F}$.^{9,10} Both $\delta^{15}\text{N}$ ⁹ and $^1\text{J}(\text{N,H})$ ³⁸ are also useful, but not used in this investigation.

The present study enables an investigation of the variation of the parameters in the model compounds especially those serving as models for the hydrazone forms, ^{19}F chemical shift and $^1\text{J}(\text{C,F})$ couplings. These data revealed that $^1\text{J}(\text{C,F})$ couplings are constant for the NH type compounds and sufficiently different from that of the azo model compound, 14, to be useful.

A similar comparison of $\delta\text{C-2'}$ and $\delta\text{C-4'}$ of the hydrazo models (16,18 and 20 for *o*-fluorosubstituted and 17,19 and 21 for the *p*-substituted) revealed that for the *o*-substituted both C-2' and C-4' showed a large difference between the hydrazo and the azo forms, whereas for the *p*-substituted only C-2' showed a sufficient difference. C-1' was not included as this resonance is not always observed and the chemical shift of C-6' turned out not to be very useful.

The compounds 22, 23 and 25 show tautomerism⁹ and so is 24 judging from the present data. The deuterium isotope effects at ^{19}F chemical shifts of 22 were found to be temperature sensitive in line with a change in the equilibrium constant towards more hydrazo form at lower temperature.^{9,10} The $^n\Delta\text{C(XD)}$ isotope effects contain both the intrinsic and the equilibrium contributions. The intrinsic isotope effects on the *p*-fluorine are very small in the azo form (15) and small in the hydrazo form (17 and 21). The chemical shift difference of the fluorine in *o*-position between the azo and the hydrazo forms can be estimated to be 7.06 ppm and similarly to 7.62 ppm for the *p*-form. The small intrinsic contributions to the isotope effect at the fluorine, as described above, makes the isotope effect at fluorine chemical shifts a very suitable probe for estimation of changes in the equilibrium upon deuteration. For the *o*-fluoro compounds 22 and 24, the correction due to the intrinsic contribution can be estimated as the weighted average of the values for 14 and 16. The mean value 0.043 is considerably larger than that for the *p*-fluorine case. The changes in the equilibrium upon deuteration of the OH/NH proton are given in Scheme 1.

24 have not previously been investigated. The percentage of hydrazone can be

estimated from the ^{19}F chemical shift^{9,10} to be 72%.

Deuteriation leads in all cases to more of the most stable tautomer demonstrating the dominant role of the hydrogen bond for the tautomeric equilibrium. However, from a comparison of the equilibrium constants with the change in equilibrium upon deuteriation no complete correlation exists between these two parameters. We observe for both pair, 22.23 and 24.25 the largest change in the equilibrium upon deuteriation for the compound with the largest equilibrium constant.

CONCLUSIONS

The intrinsic deuterium isotope effects on ^{19}F chemical shifts can be divided into three groups:

- i) Those of intramolecularly hydrogen bonded OH groups. $^n\Delta\text{F(D)}$ isotope effects are roughly proportional to those of the attached carbon and of the same sign.
- ii) The longerrange effects, which are typically through σ -bonds.
- iii) Proximity effects, which are through space (orbital overlap of non-bonded atoms) and leading to rather large positive isotope effects.

The isotope effects on ^{19}F chemical shifts can also in p-fluorophenyl substituted cases be used effectively to monitor the change in equilibrium of e.g. tautomeric systems upon deuteriation and hence to estimate the importance of hydrogen bonding.

EXPERIMENTAL

Compounds. Compounds 1.2.6.29-31 were purchased from Aldrich, Weinheim, Germany and 3 - 5 from Maybridge Chemical Compagny, Tintagel, UK. Compound 7 was synthesized from 6-fluoro-2-methoxybenzonitrile as described for 8.³¹ Compound 7 contained traces of o-hydroxyacetophenone. Compounds 9 and 10 were synthesized from the corresponding acid by esterification with methanol using H_2SO_4 as catalyst at room temperature for 5 hours. The reaction mixture was neutralized and extracted with ether. Compounds 7, 9 and 10 were red oils in small amount. Their identity were secured by ^1H and ^{13}C NMR spectra³³ and mass spectra: [m/z (%)] for 7, 154 (39), 139 (100), 83 (19), 57 (10), 43 (11); for 9, 170 (41), 139 (20), 138 (100), 110 (69), 83 (17), 82 (14), 81 (10), 57 (17); for 10, 170 (55), 139 (36), 138 (100), 110 (91), 83 (19), 82 (15), 57 (16). Compounds 11 and 13 were prepared by condensa-

tion from the corresponding β -diketones and *o*-fluoroaniline and 12 from the corresponding 2-methyl-5-fluoroaniline.³³ The compounds were distilled and recrystallized before use. 14-18 and 22-25 were prepared as described earlier in Ref. 10 and 19 - 21 were synthesized analogously to the published procedure.⁴⁰ Compounds 26 - 28 were prepared by mixing the appropriate fluoroanilines with excess of acetic anhydride and the solid product were separated and recrystallized from ethanol. 29 and 31 were synthesized as described earlier.³⁴

NMR

The ^{13}C NMR spectra of deuteriated species were recorded in CDCl_3 on a Bruker AC 250 NMR spectrometer at 62.896 Mhz with a digital resolution of 0.55 Hz per point. Chemical shifts are measured relative to internal TMS. Spectra were recorded at 300 K, in CDCl_3 unless otherwise given. Spectra of both deuteriated and non-deuteriated species, and of mixtures of the two species, were recorded for all compounds. Most low temperature spectra were recorded in CD_2Cl_2 .

The ^{19}F NMR spectra were recorded at 235.35 MHz in 10 mm tubes with a resolution of 0.6 Hz/point. ^{19}F chemical shifts are referenced to CFCl_3 .

Most of the compounds were deuteriated by dissolving the compounds in a mixture of CH_3OH and CH_3OD followed by evaporation of the solvent under reduced pressure. The degree of deuteriation could easily be varied this way.

5, 11, 12 and 13 all showed incorporation of deuterium at C-2.

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Legends to Schemes

Scheme 1. $^n\Delta F(XD)$ and $^n\Delta C(D)$, X= O or N and OH 1H chemical shifts (in italics). Hydrogen bonds are not shown to avoid overcrowding.

Footnotes to Scheme 1

- a. From Ref. 17.
- b. Given as 12.29 ppm in Ref. 17.
- c. From Ref. 33.
- d. Isotope effect due to deuteriation at carbon
- e. Taken from Ref. 30.
- f. Not observed.
- g. Coupling constants.
- h. Assignment based on carbon,fluorine coupling constant
- i. Temperature 230 K
- j. Overlap prevents determination
- k. Temperature 250 K.
- l. Temperature 225 K
- m. Temperature 280 K.
- n. Values in brackets are equilibrium constants, $K = [\text{hydrazone form}]/[\text{azo form}]$ and % change in equilibrium constant due to deuteriation.

Table 1. ¹³C chemical shifts (ppm) obtained at 300K in CDCl₃ using TMS as a internal reference.

Compounds	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8
1	119.0 ^a (5.7)	158.4 ^a (~0)	119.6 ^a (7.5)	124.8 ^a (23.2)	-	154.6 ^a (238.7)	115.3 ^a (23.0)	203.5 ^a (2.3)	26.4 ^a
2	120.2 ^a (3.8 ^b ;7.4 ^c)	147.7 ^a (13.1 ^b ;3.3 ^c)	151.5 ^a (251.7 ^b ;11.4 ^c)	111.2 ^a (21.2 ^b ;27.2 ^c)	-	153.4 ^a (10.3 ^b ;241.4 ^c)	110.7 ^a (4.2 ^b ;22.9 ^c)	204.0 ^a (N.R.) ^e	27.0 ^a
6	122.2(3.3)	149.6(12.5)	150.8(248.9)	122.6(17.5)	-	119.3(6.2)	128.4(3.5)	196.3(2.6)	-
7	N.O. ^f	163.9(4.7)	114.3(6.6)	136.2(12.7)	-	106.1(24.5)	163.4(256.1)	203.0(3.3)	32.4(11.4)
9	109.3(2.7)	163.9(14.2)	104.4(24.0)	167.4(254.0)	-	107.3(22.4)	132.2(11.5)	170.1	52.4
10	102.5(13.1)	162.9(3.5)	113.2(3.9)	135.2(12.0)	-	106.8(23.3)	162.3(260.5)	169.8(3.8)	52.5
14	137.6	150.5	117.9	131.4	-	142.9	129.9	34.2	31.4
15	136.8	150.3	117.7	130.9	-	143.0	129.6	34.1	31.4
16 ^g	-	-	148.2	129.5	-	157.5	137.7	118.3	128.7
18 ^h	162.7	127.6	199.6	26.2	-	-	-	-	-
19 ⁱ	162.8	125.9	199.1	25.8	-	-	-	-	-
20	31.7	197.9	134.5	197.0	-	26.6	-	-	-
21	31.6	198.0	133.3	196.9	-	26.6	-	-	-
22	131.0	173.4	125.1	140.7	128.2	128.6	126.1	128.9	121.8
23	129.9	166.2	123.3	138.8	128.2	128.6	125.4	128.7	121.6
24	175.8	134.0	128.1	122.0	137.2	127.7	132.7	127.1 ^j	126.5 ^j
25	169.6	132.7	128.1	120.9	136.9	127.6	131.8	126.2	126.3

Compounds	C-8a	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
1	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-
14	-	N.O. ^f	159.1(257.1)	117.0(25.6)	132.4(8.1)	124.6(3.5)	117.2(6.4)
15	-	147.3(2.9)	124.1(8.7)	116.4(22.8)	164.3(252.4)	116.4(22.8)	124.1(8.7)
16 ^e	-	129.9(9.2)	151.7(246.9)	115.7(17.9)	125.5(7.5)	124.9(3.7)	115.8(1.0)
18 ^b	-	130.4(9.1)	152.2(246.9)	116.1(12.0)	125.4(4.7)	125.1(3.5)	115.9(4.8)
19 ⁱ	-	137.8(2.8)	117.0(7.8)	116.3(22.8)	160.1(245.3)	116.3(22.8)	117.0(7.8)
20	-	N.O. ^f	152.1(246.9)	116.0(17.9)	125.9(7.3)	125.2(3.6)	116.4(3.3)
21	-	137.9(2.3)	117.7(7.6)	116.6(22.8)	160.6(247.0)	116.6(22.8)	117.7(7.6)
22	133.4	132.8(8.7)	153.9(250.7)	116.1(18.4)	127.3(7.6)	125.0(3.7)	117.0(0.8)
23	133.4	143.0(3.2)	121.2(8.6)	116.6(23.6)	162.5(249.6)	116.6(23.6)	121.2(8.6)
24	130.5	131.6(8.8)	153.1(249.1)	115.9(18.1)	126.3(7.3)	125.1(3.8)	116.7(0)
25	129.3	141.2(2.8)	120.1(8.2)	116.5(23.2)	161.9(248.3)	116.5(23.3)	120.1(8.2)

a: Ref. 17.
 b: Coupling to F-3
 c: Coupling to F-5
 d: ¹³C chemical shift for 3 - 5 and 11 - 13 are given in Ref. 33, for 8 in Ref. 31
 e: N.R.: not resolved
 f: N.O.: not observed
 g: C-9: 125.0; C-10: 11.6

H:	C-1": 137.2; C-2": 120.9; C-3": 129.1; C-4": 124.9
i:	C-1": 136.9; C-2": 120.6; C-3": 128.8; C-4": 124.6
j:	May be interchanged

Table 2 ^{19}F chemical shifts (in ppm) relative to $^{19}\text{FCl}_3\text{C}$ at 300K.

compounds	$\delta^{19}\text{F}$	compounds	$\delta^{19}\text{F}$
1	-124.56	17	-116.57 ^c
2	-131.84 ^a / -122.02 ^b	18	-132.42
3	-124.78	19	-117.32
4	-126.42	20	-132.49
5	-134.30 ^a / -124.48 ^b	21	-116.54
6	-137.17	22	-129.52
7	-105.12	23	-113.05 ^d
8	-100.21	24	-130.62
9	-101.73	25	-114.16 ^e
10	-105.59	26	-132.19
11	-122.97	27	-112.04
12	-106.95	28	-118.54 ^f
13	-122.40	29	-138.46
14	-125.12	30	-139.78
15	-109.51	31	-144.13
16	-132.84		

a: F-3

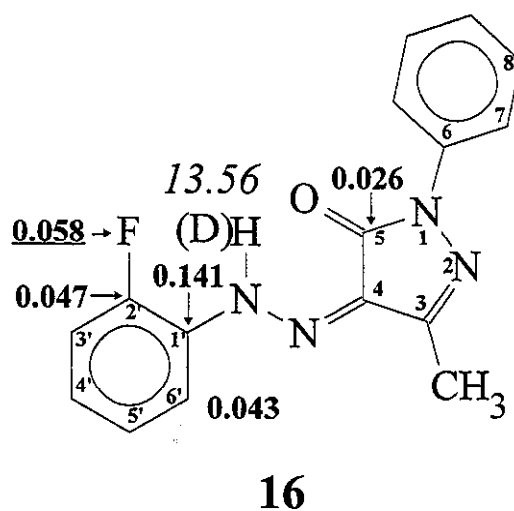
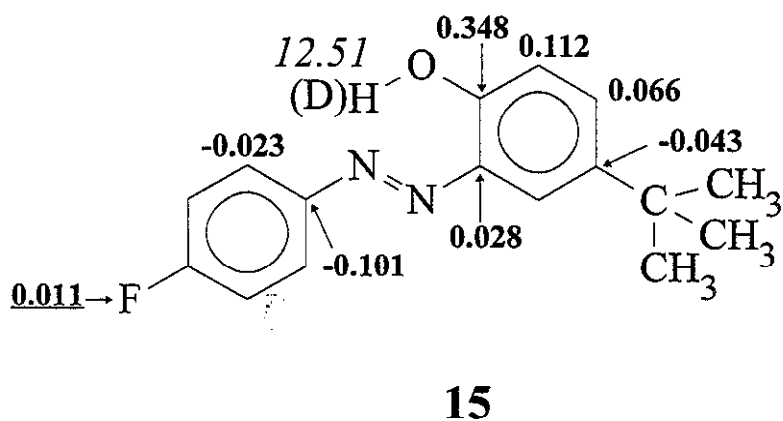
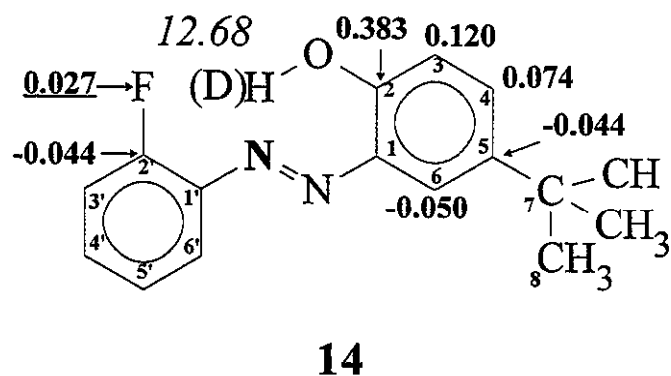
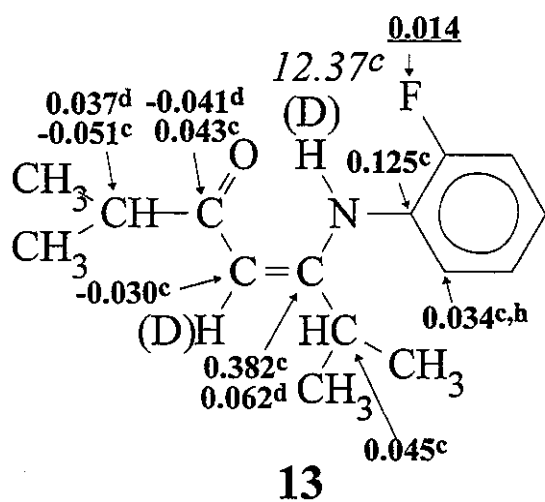
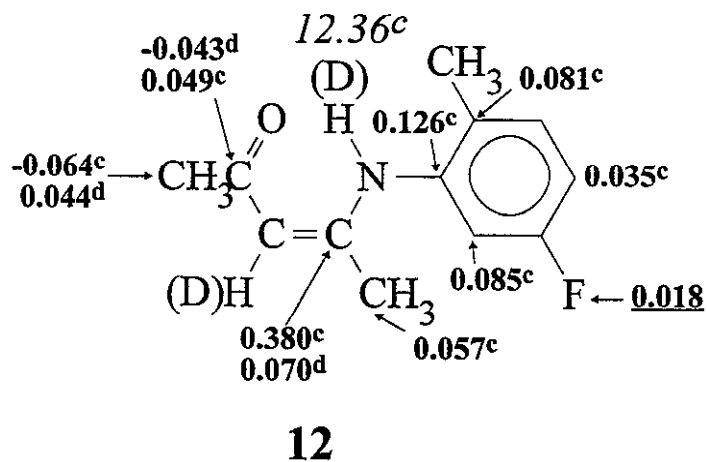
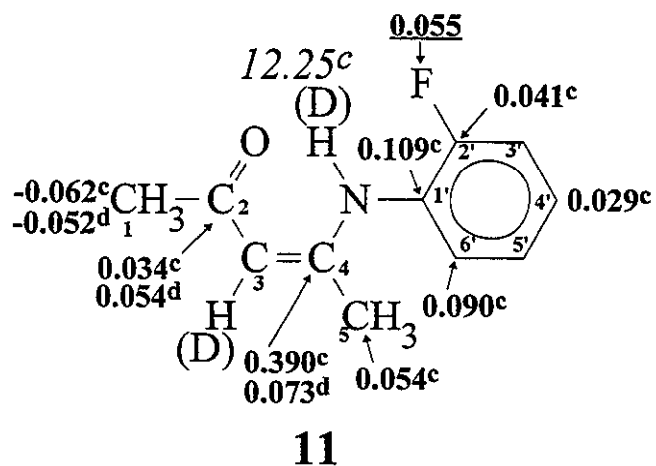
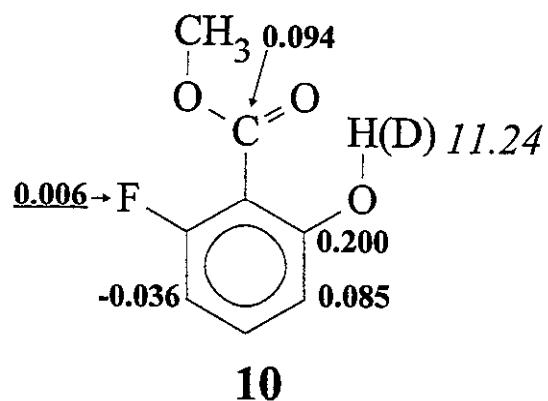
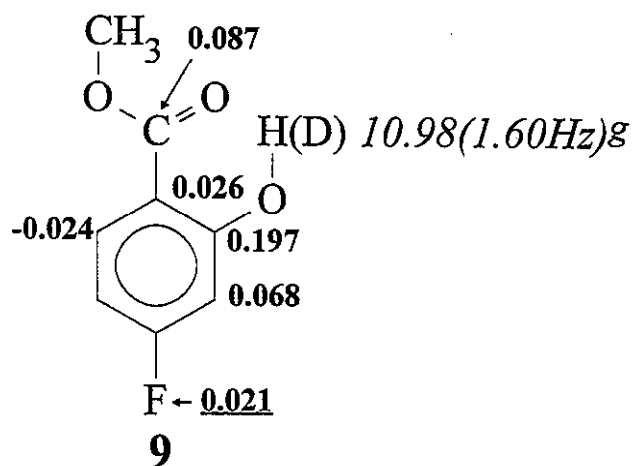
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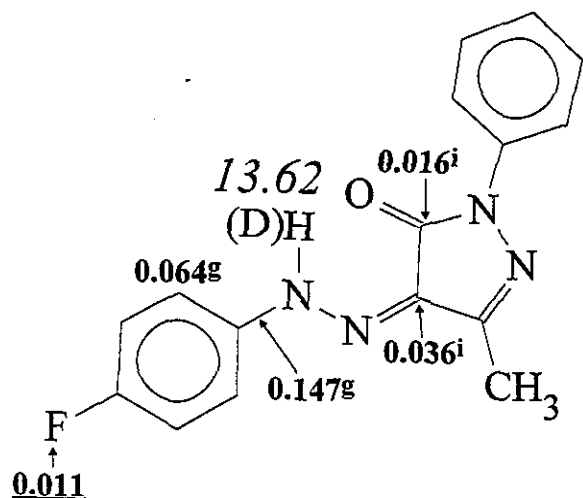
c: Ref. 9 found -116.60 and -116.47 at 310K and 290K respectively

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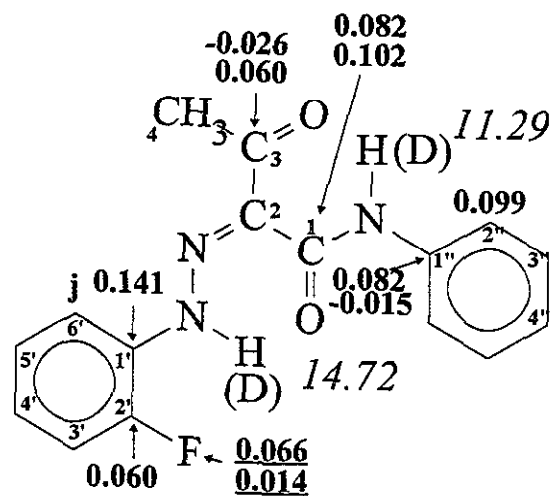
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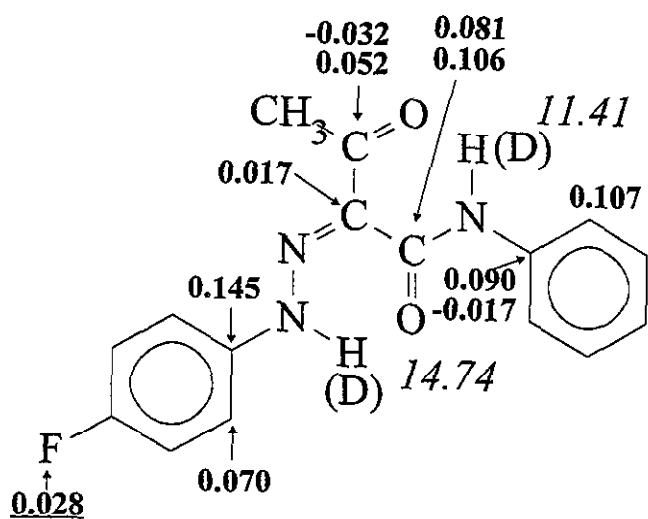




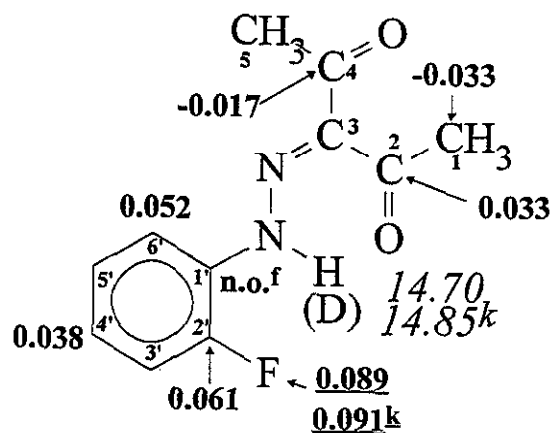
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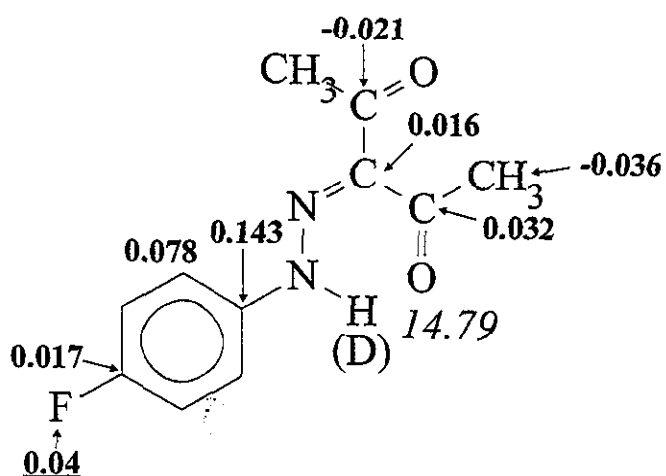
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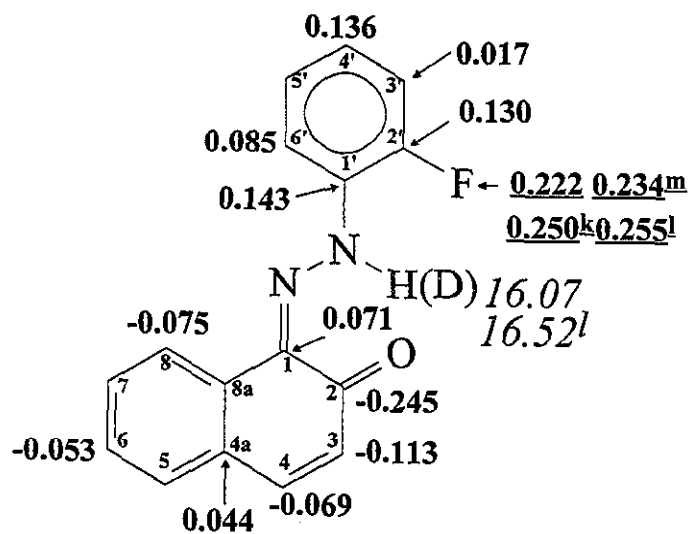
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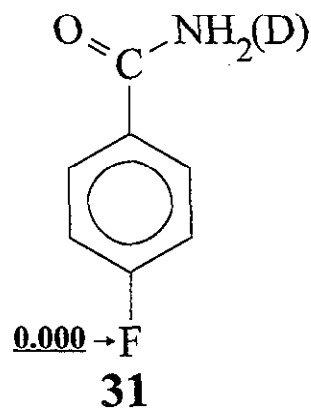
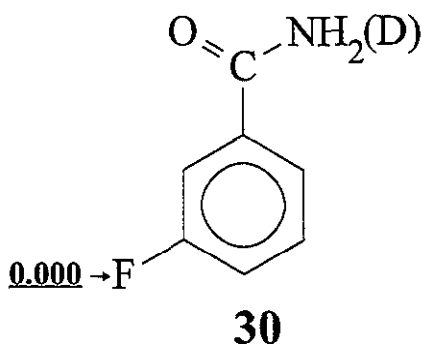
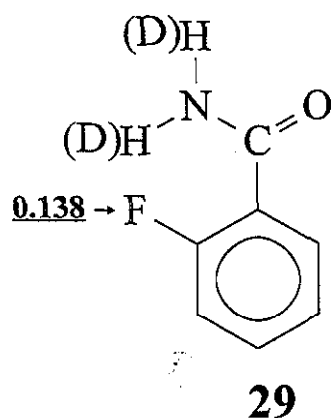
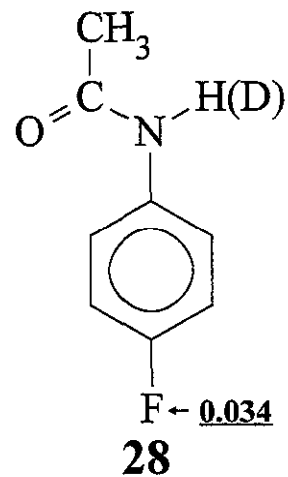
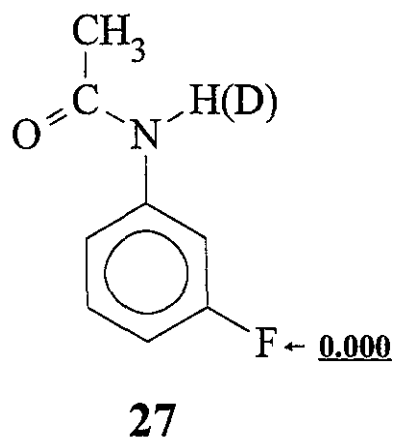
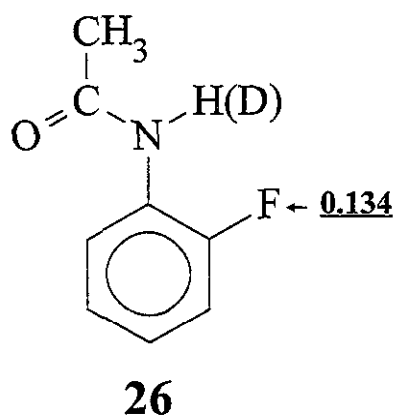
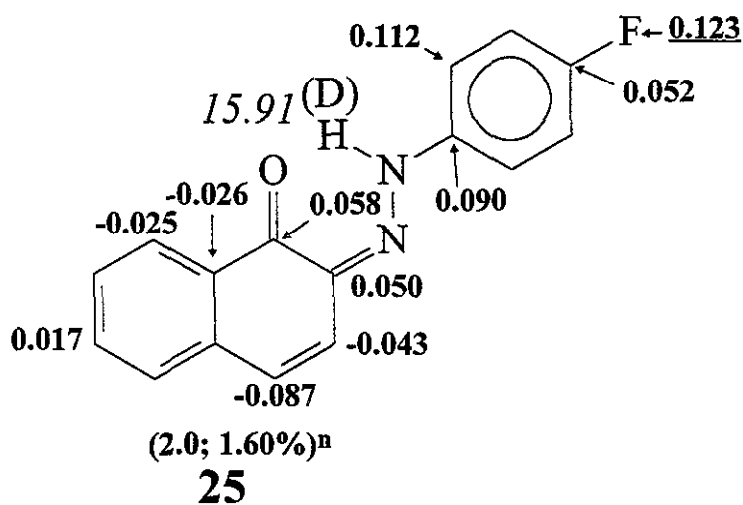
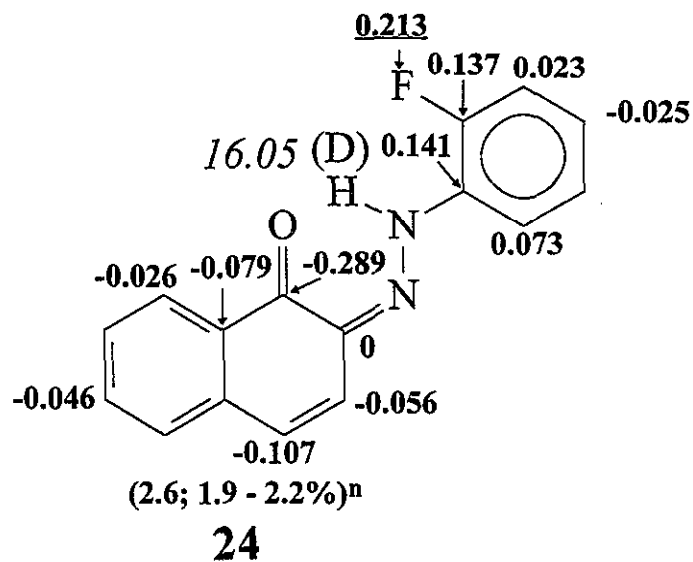
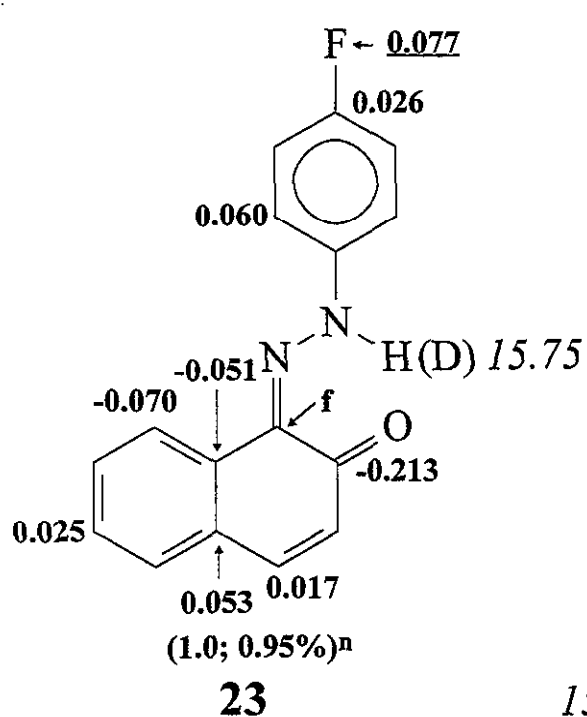


21



(1.3; 2.15-2.30%)ⁿ

22



Paper IX

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Deuterium Isotope Effects on ^{13}C Chemical Shifts of *o*-Hydroxy Acylaromatics.
Intramolecular Hydrogen Bonding.

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Keywords: Deuterium Isotope Effects, NMR, hydrogen bond dynamics, electric field effects,
tautomerism, intermolecular OH exchange

The interesting deuterium isotope effects of gossypols have been reinvestigated and the very large two bond isotope effect, $^2\Delta C-6(OD)$, is ascribed to electric field effects.

Common for the investigated compounds are the presence of intramolecular hydrogen bonds. A feature strongly related to the strength of the intramolecular hydrogen bond is intermolecular OH exchange. Electron attracting substituents at the 3- and 5-positions increase the acidity of the OH-2 proton and therefore the intermolecular exchange, but not the hydrogen bond strength, whereas alkyl groups ortho to the intramolecularly hydrogen bonded OH prevents the OH group to swing out and therefore prevents intermolecular exchange.

Conformational equilibria are studied in 1-acetyl-2-hydroxy-3-nitro-6-methoxybenzene. Surprisingly, the form with the weaker intramolecular hydrogen bond to the nitro group is dominant at ambient temperature, whereas it is opposite at 160K. For 1-acetyl-2-hydroxy-3-nitro-5-methylbenzene a similar pattern is seen, but with much less hydrogen bonding to the nitrogroup at ambient temperature.

The 2-acetyl-1,8-dihydroxy-3,6-dimethylnaphthalene is involved in tautomerism of the enolic β -diketone type and large deuterium isotope effects on the ^{13}C and OH chemical shifts are observed.

INTRODUCTION

The investigation of gossypols, (1), and related compounds revealed interesting signs of long-range isotope effects on ^{13}C chemical shifts, as well as large two-bond isotope effects¹ and therefore spurred an interest into the study of deuterium isotope effects on ^{13}C chemical shifts.²⁻⁶ In the meantime these isotope effects of *o*-acylaromatics have been thoroughly investigated.^{7,8} The effects of substituents have been mapped and the transmission mechanisms looked into.⁷ Long-range effects are seen in conjugated systems.^{4,9} Strain effects as found in, e.g. 1-acetyl-2-hydroxynaphthalene have been discussed, but the corresponding aldehydes did not show such effects.¹⁰ The very large effects found for the gossypols¹ are therefore to a large extent still unexplained.

Tautomerism of β -diketones and similar systems using deuterium isotope effects on ^{13}C chemical shifts have also been treated extensively¹¹⁻¹⁴ and the relationship between $^2\Delta\text{C}(\text{OD})$ and $^4\Delta\text{C}(\text{OD})$ ¹⁴ or $^2\Delta\text{C}(\text{ND})$ and δNH ¹⁵ have been presented, as ways of identifying tautomeric systems.

Isotopic perturbation of equilibrium showed interesting effects in symmetrical 2,6-dihydroxy acyl aromatics,^{16,17} but also in the asymmetrical compounds.^{5,16,17} The symmetrical compounds revealed that the stronger the hydrogen bond, the larger was the isotopically induced splitting, Δ_{SIP} .¹⁷ Δ_{SIP} , Splitting cause by Isotope Perturbations, which is observed for compounds where a perturbation of an equilibrium is observed. For non-symmetrical compounds, the distinction between an isotopically perturbed system and an ordinary system with two deuteria becomes more difficult and may ultimately require "freezing" of the rotation of the acyl group to resolve this ambiguity.

For the 2,6-dihydroxy compounds one OH group is momentarily non-hydrogen bonded and thus exposed to the solvent and prone to exchange.¹⁷

For weaker intramolecular hydrogen bonds the influence of solvent becomes important. Some solvents like DMSO are called hydrogen bond breaking really meaning, that a hydrogen bond is formed to the solvent and changing the hydrogen bond from an intra- to an intermolecular hydrogen bond.

One remarkable feature of some of the intramolecularly hydrogen-bonded systems is the broadness of the XH resonance despite that the δXH indicates a strong or even very a strong hydrogen bond. This feature is seen in 5-nitroaldehydes,⁶ 3- and 5-acetyl-6-methyl-

2H -pyran-2,4(3H)-diones¹⁸ and the enol form of 2-acyl-1,3-indanedione.^{19,20} This can be ascribed to increased acidity of the OH proton. The finding that for 5-substituted *o*-hydroxyacyl compounds $^2\Delta\text{C}(\text{OD})$ did not change appreciably, but δOH did, raises the important question whether the hydrogen bond is increasing in strength with the higher acidity or not. Furthermore, for the 2-acyl-1,3-indanediones the broadness was diminished by a bulky substituent at the C-1 carbon.¹⁹ For aromatic systems the influences of bulky substituent can be investigated by substitution at the *o*-carbon.

Deuterium isotope effects on ^{13}C chemical shifts represent a useful tool to characterize the structure and dynamics of *o*-hydroxy acyl aromatic and olefins covering a broad range of compounds: *o*-hydroxyacetophenones, *o*-hydroxybenzaldehydes and *o*-hydroxybenzoic esters,^{5,7,10,17} 2-acyl-1,3-indanediones,^{19,20} linderones and lucidones,⁶ enamines,^{15,20,21} enaminoesters.^{15,20}

The present paper demonstrates how the above described phenomena, steric strain, isotopic perturbation of equilibria, tautomerism and ordinary hydrogen-bonded systems may be distinguished by means of deuterium isotope effects on ^{13}C chemical shifts.

ASSIGNMENTS

The ^{13}C chemical shifts are given in Table 1. The assignment of the ^{13}C spectra of **1** is that of Ref.1 and the assignment of **2** is similar to those of the hemigossypolones of the same reference. The assignments of **3 -12**, **14 - 16** and **17 - 20** are based on substituent effects. In case of **14** the starting parameters were those of 7-hydroxycoumarin.²² The spectra of **7** at ambient temperature are clearly the result of an equilibrium. The low temperature spectra of **7** showed two sets of resonances, an intense set, **7A** (see Results) and a very weak one, the **B** form. In the same way the OH resonances were assigned. The assignment of **13** is based on HETCOR spectra.²³ The OH resonances were assigned so that OH-1 is at highest frequency. The C-3 resonance of **17** can be assigned unambiguously as it shows two equally large isotope effects due to symmetry. The assignment of **21** was done in analogy with that of 1-phenylazo-2-naphthol.²⁴

The determinations of signs of isotope effects are done by varying the degree of deuteration. For those compounds with more than one exchangeable hydrogens the assignment of isotope effects due to specific deuteria could be done for **4** and **18**. In the former case the ND group did not give rise to an isotope effect and for **18** the degree of incorporation was distinctly different from that of the OH group. For compounds **1**, **2**, **10**, **11** and **13** comparisons were made with well established substituent effects.

RESULTS

As indicated above the deuterium isotope effects on chemical shifts and OH chemical shifts are the central theme of this paper (Scheme 1). The isotope effects are defined as ${}^n\Delta C(D) = \delta C(H) - \delta C(D)$, n being the number of intervening bonds between the nuclei observed and the isotope in use. The isotope effects have been measured in one tube experiments with both isotopomers present and the experiments were repeated if necessary with different H:D ratios.

The isotope effects of **1** have been reinvestigated. **1** is not very soluble in neither $CDCl_3$ or CD_2Cl_2 , so the data of **1** are obtained in acetone- d_6 at low temperature in a mixture of the isotopomers. This is in contrast to those of Ref.1 recorded at ambient temperature. At ambient temperature fast intermolecular exchanges occur and one obtains the sum of isotope effects, not the individual contributions from each deuterium. Except for C-7 the isotope effects differ considerably (Scheme 1). The very large ${}^2\Delta C-6(OD)$ isotope effect (0.85 ppm) is remarkable as the corresponding isotope effect of 2-hydroxy-1-naphthaldehyde is 0.41 ppm.⁷ The remaining isotope effects due to OD-6 are "normal". The two other OD groups give only rise to local effects over two and three bonds (Scheme 1).

Gossypolone **2** was too insoluble at low temperature to be able to measure deuterium isotope effects on ${}^{13}C$ chemical shifts.

Compound **3** showed that methyl substitution at position 4 had a very moderate effect at the isotope effects as compared to 2-hydroxyacetophenone.⁷ The isotope effects of **4** were changed as expected for an electron donating substituent at position 4 and are similar to those of 4-methoxy-2-hydroxyacetophenone.⁷ Compound **6** had to be cooled to show isotope effects on ${}^{13}C$ chemical shifts.

The OH chemical shift of **5** was to higher frequency compared to 2-hydroxyacetophenone. ${}^2\Delta C-2(OD)$ was likewise increased. This can be ascribed to the steric compression effect of the t-butyl group at C-3. The effect of the t-butyl group at C-5 is likely to be unimportant.

The ambient temperature spectra of **7** gave sharp resonances, but rather unusual deuterium isotope effects at ${}^{13}C$ chemical shifts. Both the OH and the ${}^{13}C$ chemical shifts varied considerably with temperature until 170 K at which temperature two sets of resonances appeared. The low frequency OH resonance at 11.15 ppm was broad and not very strong.

The intensity ratio was larger than 10:1 at 170 K. At 160 K the low frequency OH resonance sharpened. The ^{13}C spectrum at 160 K showed also two sets of resonances (Table 1). The resonances of the minor form are broad and not very intense and no isotope effects could be determined for this form. The ^{13}C chemical shifts of the two forms are rather different, and with those of the minor form generally to lower frequency (Table 1). The two sets of resonances can be ascribed to the two isomer **7A** and **7B** (Fig. 1). The C=O resonance of the major form showed a relatively large isotope effect of 0.19 ppm at 160 K and this effect demonstrates clearly that this is the isomer with an intramolecular hydrogen bond to the carbonyl group (**7A**). Analysis of the OH and ^{13}C chemical shift at 300 K revealed that the form **7B** with a hydrogen bond to the nitro group was the dominant (64%). At 250 K the two forms were of almost equal amounts. Further cooling broadened the OH resonance and moved it further to higher frequency. At 220 K the **7A** form dominates (56%).

Knowing the chemical shift differences between carbon resonances of forms A and B, the isotope effects of form A and being able to estimate those of form B based on the data of compounds **19** and **20**, the shifts in the equilibrium upon deuteration can be estimated to ~4% at 300 K and ~4.6% at 250 K.

The ^1H spectrum of **8** showed an increase in the chemical shift of the OH resonance from 12.82 at 300 K to 13.62 K at 180 K, but also line broadening in the temperature range 220 to 200 K. In the temperature range 300 to 230 K a linear dependence with temperature was found with a coefficient of 0.008 ppm/degree. The ^{13}C spectrum showed likewise a modest temperature dependence. The C=O, C-1 and C-3 resonances broadened around 220-200 K only like the OH resonance to become sharp at 180 K.

The isotope effects of **9** have previously been published.^{5,10} In this study, the compound is cooled to slow down OH exchange and give precise isotope effects. For **10** and **12** substitution at positions 3 - 5 are further investigated. The data of **10** showed that an extra OH group at position 3 had only a small effect at the $^2\Delta\text{C}(\text{OD})$ (see discussion of gossypols).

The very high frequency OH shift of **13** (17.42 ppm) is remarkable (Scheme 1) as the corresponding 1-hydroxy-2-acenaphthone has a δOH of 13.99 ppm.⁷ Also the second OH was sharp (10.16 ppm). Likewise, both OH resonances of **13** showed very large isotope effects, when the other OH group was deuteriated (Scheme 1). The situation is somewhat akin to that seen for 2-hydroxydibenzoylmethane.⁸

The C-1,C-2,C-3 and C-5 resonances of the ^{13}C spectrum **17** are sharp at ambient temperature, whereas those of the C=O and C-4,C-6 carbon resonances are broad. The $^2\Delta\text{C(OD)}$ isotope effect is only marginally larger than that of salicylaldehyde.^{1,4,5,7,10}

The $^2\Delta\text{C(OD)}$ isotope effect for **14** is interesting as **14** structurally is similar to 2-hydroxy-1-acenaphthone¹⁰ with the one difference that no steric interaction exists between the $\text{CH}_3\text{C=O}$ group and O-1 in **14**. The long-range effects of **14** are to a certain extent similar to those observed for khellinone,⁷ showing that the transmission of the isotope effect into the double bond is a common feature.

As reference parameters for **7** the *o*-nitrophenols **19** and **20** were recorded. Both showed small two-bond isotope effects of the order of 0.183 ppm (**19**) and 0.140 ppm (**20**) and the latter showed broad resonances at 180K. The latter value is in line with the finding for *o*-hydroxy acyl aromatics that an extra nitro group leads to a decrease of $^2\Delta\text{C(OD)}$ (see later).

Finally, the formally 1-nitroso-2-hydroxynaphthalene (**21**) was investigated. The results showed, that this compound existed as the keto-imine - hydroxy-nitroso tautomeric mixture. The isotope effects are almost constant with temperature.

^1H OH chemical shifts. OH chemical shifts are generally given in Scheme 1. For those compounds not mentioned in Scheme 1, the OH chemical shifts are for gossypolone (**2**), $\delta\text{OH-6} = 12.65$ ppm and $\delta\text{OH} = 10.18$ ppm at 193 K in acetone- d_6 . 3-allyl-2,6-dihydroxyacetophenone (**15**), $\delta\text{OH-2} = 10.84$ ppm $\delta\text{OH-6} = 8.62$ ppm at 220 K in CD_2Cl_2 and for 3-propyl-2,6-dihydroxyacetophenone (**16**) $\delta\text{OH-2} = 11.92$ ppm and $\delta\text{OH-6} = 7.85$ ppm at 300 K in CDCl_3 .

DISCUSSION

Gossypols

Gossypol has been investigated in great detail because of its interesting biological properties.^{26,27} It has been established that gossypol can exist as a lactol in DMSO, CH_3CN , ethanol and methanol,^{26,27,28,29} but also in a tautomeric equilibrium.^{26,28} In chloroform a tautomeric equilibrium (Fig. 2) has been suggested,³⁰ long ago. The $\Delta\text{OH-6}$ of gossypol and hemigossypol¹ (~ 15.3 ppm in acetone- d_6) and a large $^2\Delta\text{C-6(OD)}$ of 0.8 ppm could suggest a tautomeric equilibrium,¹¹⁻¹⁴ but the lack of isotope effect at C-11 is against a tautomeric

equilibrium. *o*-Hydroxyaromatic aldehydes generally show very small isotope effects at the aldehyde carbon.^{3,9} For tautomeric systems as found in Ref.2 a large effect is clearly seen both at the C-OH and the aldehyde carbon in CDCl₃. Both findings suggest that **1** is non-tautomeric.

Another explanation emerges from a comparison of ¹³C chemical shifts of hemideoxygossypol³¹ and hemigossypol.¹ No major differences in chemical behaviour are found between gossypol and hemigossypol.¹ The chemical shifts of C-5, C-6 and C-7 are very similar, whereas that of C-11 of hemigossypol is 5.1 ppm to higher frequency. This suggests a local interaction involving the aldehyde group. The OH group at C-4 may lead to a mesomeric strengthening of the acidity of OH-6. This is also supported from the tendency to intermolecular exchange of this proton. However, the very large effect cannot be explained by this effect,¹⁰ as this is also found in the 7-methoxyderivative. However, the OH position at high frequency and the large ²ΔC-6(OD) of hemigossypol and gossypol can be understood as the OH group at positions 4 leads to a more acidic OH-6 group, but more importantly to a polarization of the C=O aldehyde group due to an electric field and may by steric effects, thus effectively leading to more of the resonance form C, shown in Fig. 2

Equilibrium Isotope Effects

Compound **7** showed a sharp OH resonance and gave some unusual isotope effects that cannot be explained by straightforward effects of the substituent as discussed above. The very large effects at all carbons except the methyl group (relative to 2-hydroxyacetophenone) can be understood as an isotopic perturbation of the equilibrium as shown in (Fig. 1). The deuterium isotope effects have to be analysed accordingly. Using the OH chemical shifts and the intensities at low temperature the B form is dominant at ambient temperature, but the amount of this form is very small at 160 K. The spectra at 160 K gave a ²ΔC(OD) of 0.46 ppm for the **7A** isomer. Most of the isotope effects at ambient temperature do clearly have a positive equilibrium component. As the A form have chemical shifts to higher frequency than the B form (Table 1), the B form is being increased upon deuteration. This is even more so at 250 K and 230 K although the amount of B isomer is decreasing. This can be explained by realising that the mole ratio for A changes from 0.36 at 300 K to 0.56 at 220 K. This will increase the change in equilibrium upon deuteration as seen by plotting these number into the

graph of Fig. 7 of Ref.14.

The finding that the amount of the dominant tautomer, B, at ambient temperature, is not increased further at low temperature is rather unusual. This can be explained by assuming that the ΔS for 7B is positive and large enough to overcome the difference in ΔH due to a much weaker intramolecular hydrogen bond at ambient temperature. The more positive ΔS of 7B can be understood as the nitro group of 7A most likely is subject to hindered rotation due to conjugation (see later). The rotation of the acetyl group of 7B therefore gives rise to a positive ΔS . For 8 the picture is less clear.

Intermolecular exchange

Line broadenings may occur in compounds like the ones studied either because of intermolecular exchange or averaging. An example of the latter is that of 2,4,6-trihydroxy-3,5-diacetylbenzene.³²

From the study of 5-nitrosalicylaldehyde⁶ it became clear that this compound had to be cooled to show a sharp OH resonance and to give deuterium isotope effects on ^{13}C chemical shifts. This can most likely be related to the higher acidity of the OH proton. Of the pair 19 and 20 the former gave a sharp OH resonance at ambient temperature, whereas the latter had to be cooled. The pK_a values are 7.23 and 3.70, respectively.^{33,34} It is interesting to notice, that the increase in δOH upon nitro group substitution is much smaller in 6 and 18 compared to the non-nitrosubstituted compounds (4-methoxy-2-hydroxyacetophenone and 4), than it was in 5-nitrosalicylaldehyde vs. salicylaldehyde.⁷ For the two former a decrease in $^2\Delta\text{C}(\text{OD})$ with introduction of a nitro group is observed, whereas for 5-nitro- vs. salicylaldehyde $^2\Delta\text{C}(\text{OD})$ remained constant. For 7A a large increase in δOH and a medium one of $^2\Delta\text{C}(\text{OD})$ are observed resulting in a position below the correlation line of Fig. 3 (see later). Summarising, a nitro group in position 3- or 5 increases the acidity of the OH-2 proton and shifts this resonance to a higher frequency, but the hydrogen bond strength, as judged from $^2\Delta\text{C}(\text{OD})$ does not increase at best it is unaltered. An acyl group is also expected to lead to effects similar although slightly smaller than those of a nitro group. This is seen for 2,4-dihydroxy-1,5-diacetylbenzene³² for which it was necessary to cool the sample, but not for the corresponding 3-ethyl derivative.³² Likewise, for 18 isotope effects could be obtained at ambient temperature. A common feature for 2,4-dihydroxy-3-ethyl-1,5-diacetylbenzene³² and

18 is the position of an alkyl group ortho to the OH group. According to the base catalysed exchange of a hydrogen-bonded OH group the hydroxy group has to move away from the acceptor before exchange can take place.^{35,36} In the present compounds the o-alkyl group makes this step much less likely and therefore slows intermolecular exchange. The effects of alkyl groups are also demonstrated in **5** in which the hydrogen bond becomes stronger. The effects of alkyl groups are also seen on the nearly symmetrical compounds **15** - **16**. For **16** two broad OH resonances are observed at 11.92 and 7.75 ppm indicating that the alkyl substituent is close to fixing the carbonyl in a hydrogen bond to OH-2. Alkyl substitution at C-3 was in the case of a *t*-butyl group (**5**) seen to increase both δOH and $^2\Delta\text{C-1(OD)}$ and therefore also the hydrogen bond strength. A similar feature is found for **16** and to a lesser degree for **15**.

Tautomerism

The ^{13}C chemical shifts of **13** points towards a dominating carbonyl character of the C=O group. The deuterium isotope effects at the carbon chemical shifts are large for C-1, C=O, $\underline{\text{CH}_3}\text{C=O}$, C-8 and C-4a. The sum of two bond, $^2\Delta\text{C(OD)}$, and the four bond, $^4\Delta\text{C(OD)}$, isotope effects is 0.91 ppm, which points towards a tautomeric system.¹⁴ Another feature of this compound is the steric interference between the $\text{CH}_3\text{C=O}$ group and the methyl group at C-6. This could lead to strain effects.¹⁰ However, a comparison of the effect of **13** with those of 2-hydroxy-1-acetophenone and similar compounds¹⁰ reveals distinct differences. A comparison with o-hydroxydibenzoylmethane shows resemblance.⁸ In the latter case, the sum of $^2\Delta\text{C(OD)}$ and $^4\Delta\text{C(OD)}$ is also less than the 1.2 ppm suggested as a lower limit for tautomerism in six-membered rings.¹⁴ The δOH is much lower in the strained compounds and the isotope effects at the $\underline{\text{CH}_3}\text{CO}$ group is really much smaller in the strained compound. This taken together with the remaining large and some negative isotope effects points clearly towards a tautomeric system. This is also supported by plotting the $^2\Delta\text{C(OD)}$ vs. $^4\Delta\text{C(OD)}$ into Fig. 7 of Ref. 20. This shows clearly, that the point falls off the line. One favourable interaction is that between the OH group at C-8 and the enolic β -dicarbonyl system of C-1, C-2 and C-7.

The data of **21** can be compared to those of o-hydroxyazobenzenes and show clearcut tautomerism between keto-imine hydroxy nitroso forms.

CONCLUSIONS

The unusually large $^2\Delta\text{C-6(OD)}$ of **1** has been explained as originating from an electric field polarisation of the aldehyde C=O bond caused by the OH group at C-4.

Nitro or acetyl groups in *o*- or *p*-positions to the OH group clearly increases the acidity of the OH group and shifts the OH resonance to higher frequency to an extent depending on the presence of other substituents. The $^2\Delta\text{C(OD)}$ isotope effects are not increased and therefore, the hydrogen bond is not strengthened.

Alkyl group *ortho* to the intramolecularly hydrogen bonded OH group diminishes intermolecular OH exchange and stabilises the intramolecular hydrogen bond.

Tautomerism may be established using $^n\Delta\text{C(OD)}$ isotope effects as found in **13**. Further, deuterium isotope effects are likewise found to reveal hydrogen bond dynamics not seen by ordinary NMR measurements as demonstrated for **7**. The rotamer equilibrium involving the OH group hydrogen bonding both to the acyl and the nitro group is immediately apparent.

EXPERIMENTAL

Compounds

Compounds **1** and **2** were purchased from Sigma, **3-8**, **13-14** and **18** from Maybridge, Tintagel, UK; **8-12**, **16**, **19-21** from Aldrich, Weinheim, Germany and **17** from Tokyo Kasei Kogyo, Chuo-ku, Japan. These products were used without further purification.

NMR

The ^{13}C NMR spectra of deuteriated species were recorded in CDCl_3 on a Bruker AC 250 NMR spectrometer at 62.896 MHz with a digital resolution of 0.55 Hz per point. Chemical shifts are measured relative to internal TMS. Spectra were recorded at 300 K, in CDCl_3 unless otherwise given. Spectra of both deuteriated and non-deuteriated species, and of mixtures of the two species, were recorded for all compounds. Most low temperature spectra were recorded in CD_2Cl_2 .

The HETCOR spectra²³ were recorded as previously described in Ref. 17.

Deuteration

Most of the compounds were deuterated by dissolving the compounds in a mixture of CH_3OH and CH_3OD followed by evaporation of the solvent under reduced pressure. The degree of deuteration could easily be varied this way.

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Legends to Figures and Schemes

Figure 1

Rotamers and resonance form of 7.

Figure 2.

Tautomers and resonance forms of gossypol (**1**).

Figure 3.

δOH vs. $^2\Delta\text{C(OD)}$

a is **1** and b is **20**.

Scheme 1. Deuterium isotope effects on ^1H and ^{13}C chemical shifts and OH chemical shifts (in italics) for **1** - **19**.^a

Footnotes to Scheme 1.

- a. Hydrogen bonds not shown to avoid overcrowding.
- b. Temperature 220 K. Values are due to deuteration at OH-6, if nothing else is given.
- c. Due to deuteration at OH-4.
- d. Due to deuteration at OH-7.
- e. Temperature 200 K.
- f. Assignment tentative.
- g. Values in square brackets from reference 1.
- h. Temperature 180 K.
- i. No deuterium isotope effects on chemical shifts could be observed due to deuteration at this NH group.
- j. Temperature 220 K.
- k. Temperature 300 K.
- l. For hydrogenbonding of OH group see text.
- m. Solvent CDCl_3 .
- n. Solvent CD_2Cl_2 .
- o. n.o. means not observed.

- p. Temperature 250 K.
- q. Temperature 220 K.
- r. Temperature 160 K.
- s. Not all isotope effects could be observed due to poor S/N ratio caused by the low solubility of the compound at 160 K.
- t. Isotope effects could not be measured due to effects of footnote s and very low occurrence of this isomer.
- u. Temperature 260 K.
- v. Numbers in bracket are isotope effects due to deuteration at OH-2'.
- x. Trace of DMSO-d₆ added to improve the solubility.
- y. Assignment tentative.
- z. Isotope effect due to deuteration at OH-2.
- aa. Only the very large isotope effects are observed probably because of OH exchange.
- bb. Compound showed tautomerism. See text. Isotope effects are due to deuteration at OH-1, if nothing else is given.
- cc. Isotope effect due to deuteration at OH-8.
- dd. Values in brackets are deuterium isotope effects at OH chemical shifts caused by deuteration at the other OH group.
- ee. Isotope effects could not be measured at CD₂Cl₂ due to insolubility at low temperature.
- ff. Temperature 310 K.

Table 1. ¹³C chemical shifts (ppm) obtained in CDCl₃ using TMS as a internal reference.

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Others	temp. (K)
3	117.6	162.5	118.4	148.0	120.2	130.6	203.9	26.5	21.9(CH ₃)	300
4	111.1	161.8	110.9	152.3	101.7	130.8	201.3	25.7	37.9/14.8(HNCH ₂ CH ₃), 14.3/20.9/24.6 (CH ₂ CH ₂ CH ₃)	300
5	118.8	160.1	138.1	131.4	140.1	124.4	205.2	27.1	35.2/34.3(C), 31.4/29.4((CH ₃) ₃ C)	300
6	112.1	~167.5	101.4	159.6	130.9	130.4	202.5	26.2	56.9 (OCH ₃)	300
7	116.9	156.9	129.3	131.1	103.3	164.8	202.6	33.2	57.2 (OCH ₃)	300
7	115.3	157.6	130.2	131.8	103.1	165.0	203.7	33.7	57.2 (OCH ₃)	250
7	n.o. ^a	br. ^b	130.2	132.2	103.0	165.2	204.2	33.9	57.3(OCH ₃)	230
7A	110.5	161.3	128.8	134.9	101.9	166.8	207.2	-	-	160
7B	119.2	152.9	~134.9	130.7	104.8	163.1	201.9	-	-	160
8	122.3	154.0	137.0	128.2	131.6	137.0	202.8	28.1	20.2 (CH ₃)	300
10	113.1	152.5	151.4	151.4	107.3	126.3	200.5	-	138.3 C-1', 128.9 C-2', 128.2 C-3', 131.4 C-4'	300
11	112.6	165.8	103.3	164.5	107.8	135.5	198.6	-	129.5 C-1', 131.5 C-2', 115.2 C-3', 160.9 C-4'	300
12	118.1	161.7	120.5	145.6	124.1	132.8	200.2	-	20.8(CH ₃), 137.5 C-1', 129.0 C-2', 128.5 C-3', 132.1 C-4'	300
13	169.0	113.2 ^c	133.4	117.4	121.4	138.5	112.7	158.2	143.9 C-4a, 111.1 ^c C-8a, 204.8 C=O, 32.1 COCH ₃ , 22.0 ^c (CH ₃), 25.3 ^c (CH ₃)	300
14	-	159.5	111.2	153.1	131.3	115.2	166.7	109.5	112.0 C-4a, 155.3 C-8a, 204.5 C=O, 34.0 COCH ₃ , 19.2 (CH ₃)	300

15	110.2	160.3	118.4	136.8 ^c	107.1	159.0	205.8	33.9 ^c	33.5 ^c /136.4 ^c /116.4 (CH ₂ -CH=CH ₂)	300
16	110.0	160.8	121.8	136.6	106.3	157.6	205.9	33.5	31.2/22.7/13.9 (CH ₂ CH ₂ CH ₃)	300
17	122.8	161.6	122.8	137.8	129.4	137.8	192.1	-	19.9 (CH ₃)	300
18	111.2	165.7	116.0	150.5	n.o. ^a	130.4	202.4	25.9	42.2/16.3(HNCH ₂ CH ₃)	300
19	155.2	133.7	125.1	120.2	137.6	120.0	-	-	-	300
20	148.7	136.0	131.7	118.5	131.7	136.0	-	-	-	180
21	144.5	182.5	125.5	147.7	129.5	130.8	129.4	122.8	128.3 C-4a, 130.4 C-8a	300

a. N.o. means not observed
b. Br. means broad
c. May be interchanged

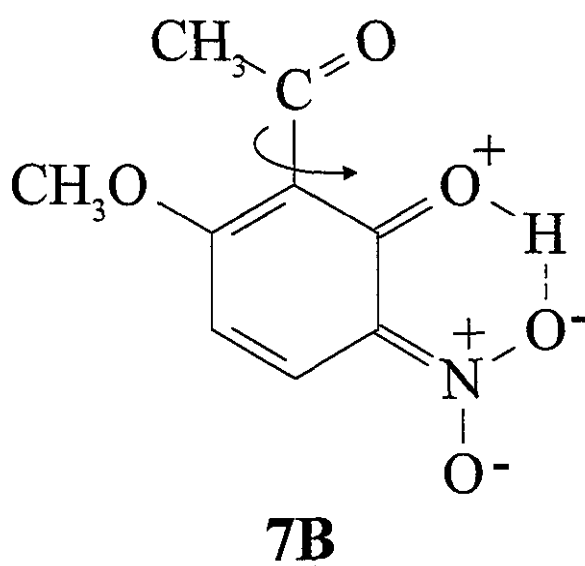
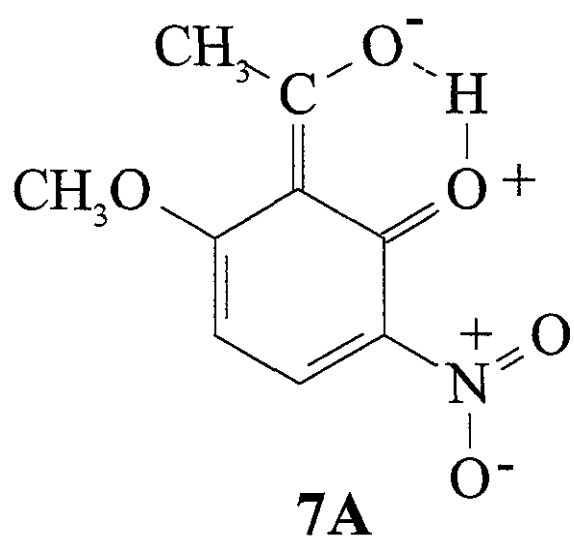
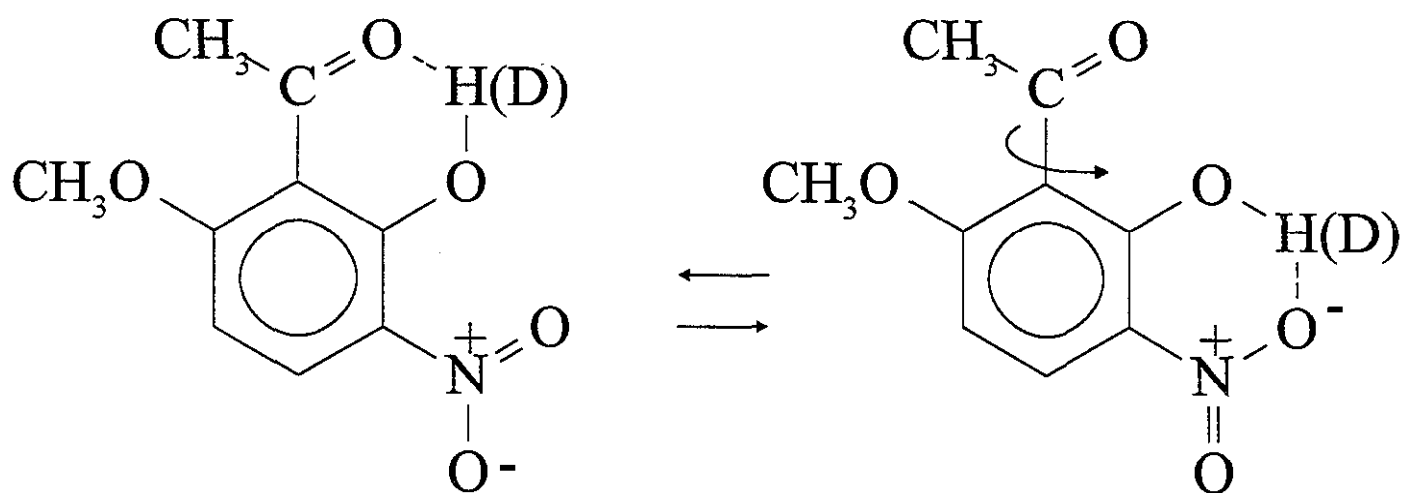


Fig. 1

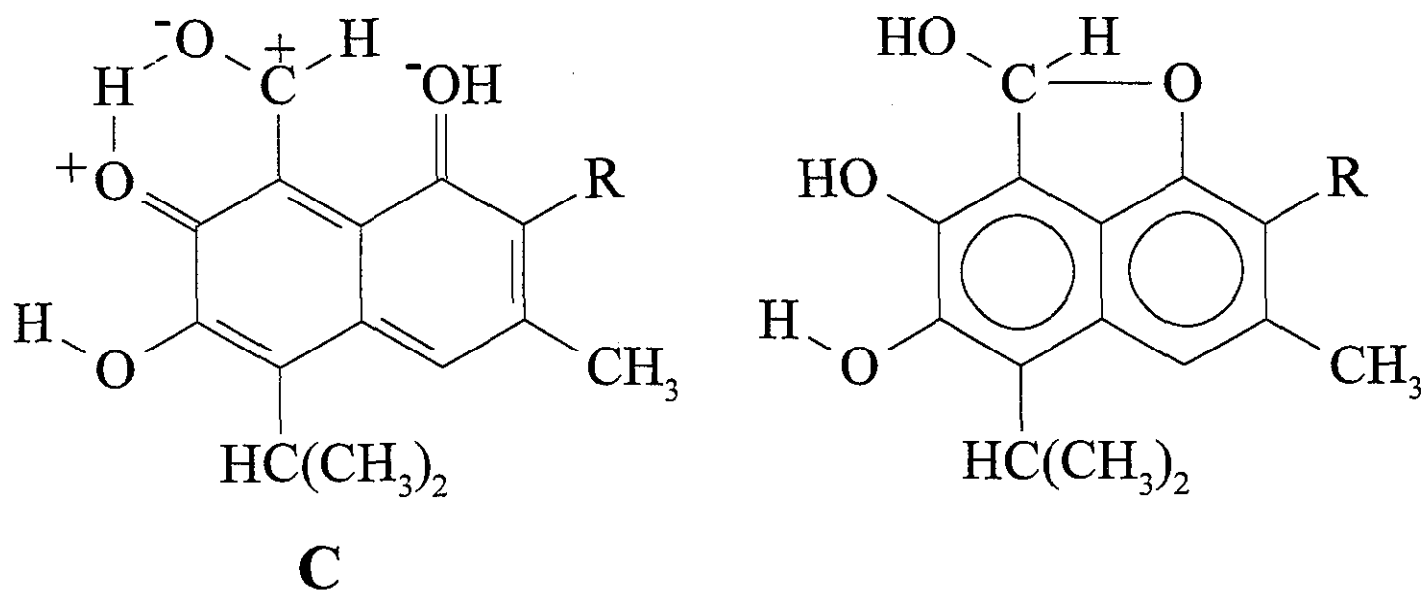
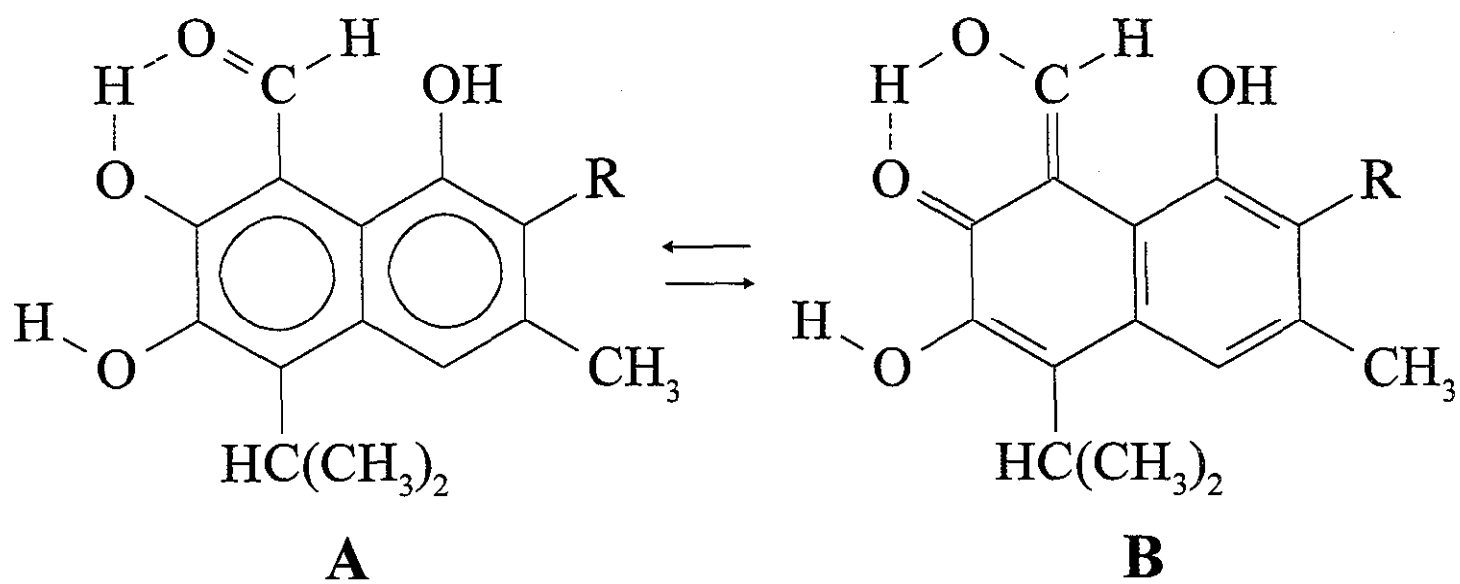


Fig. 2

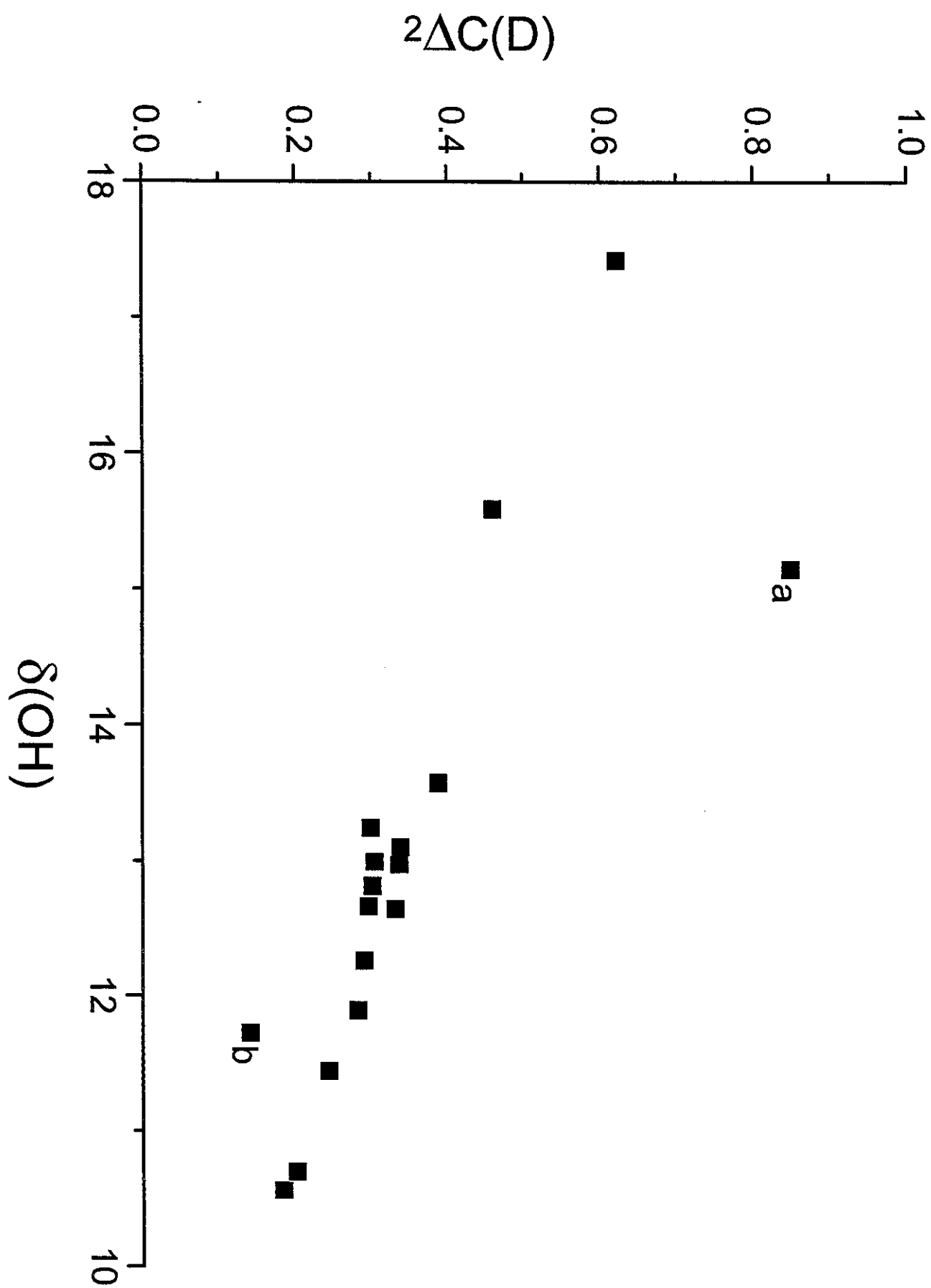
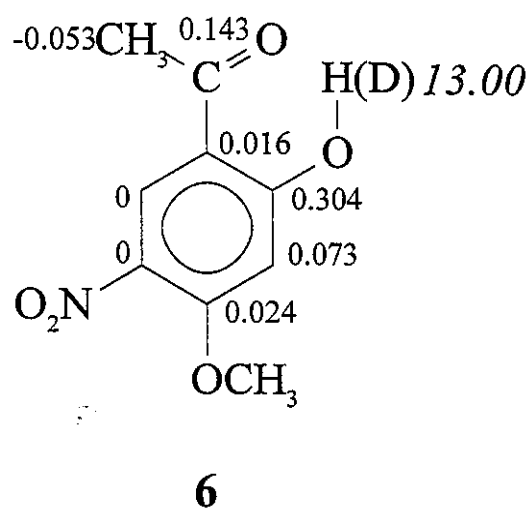
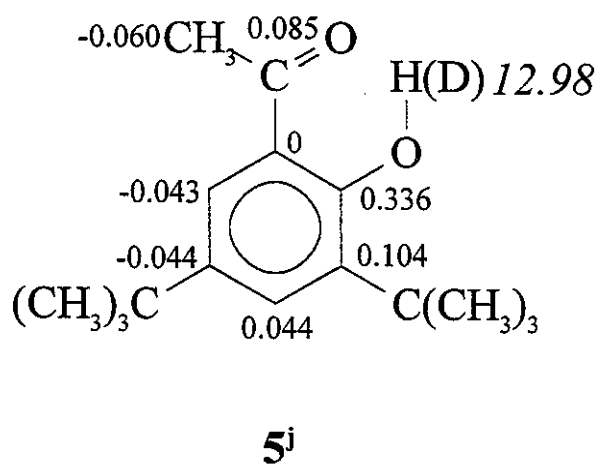
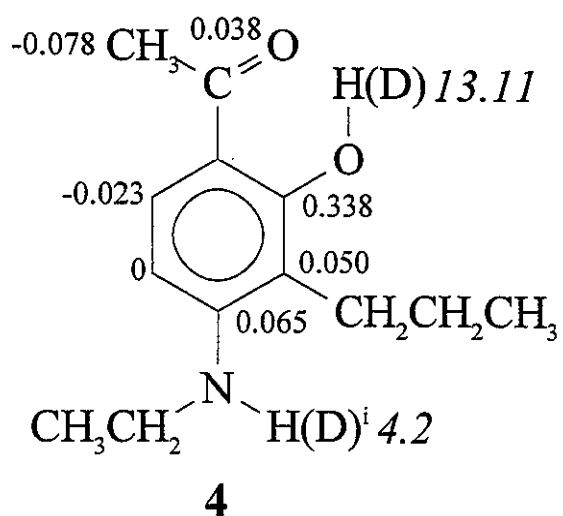
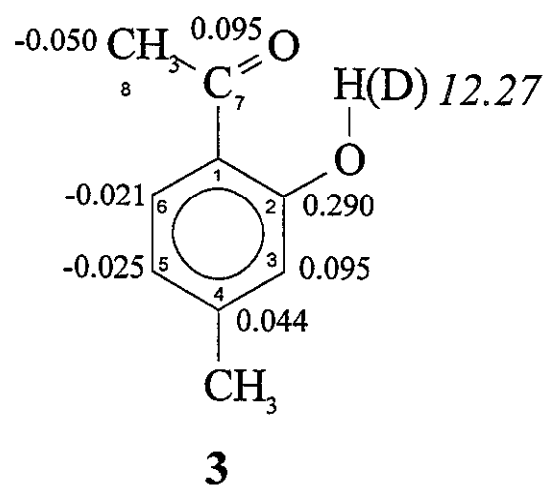
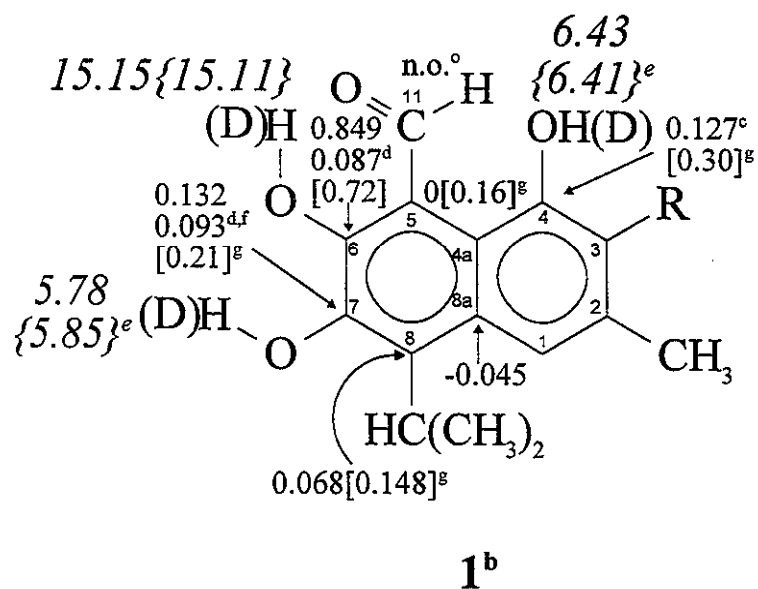
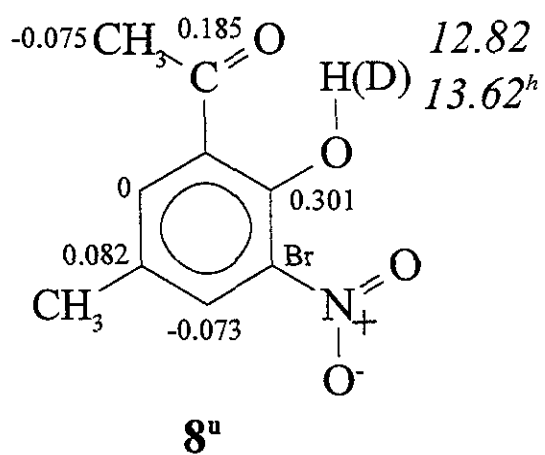
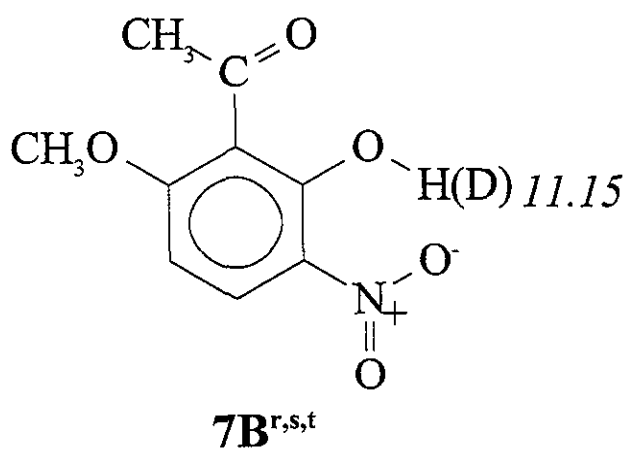
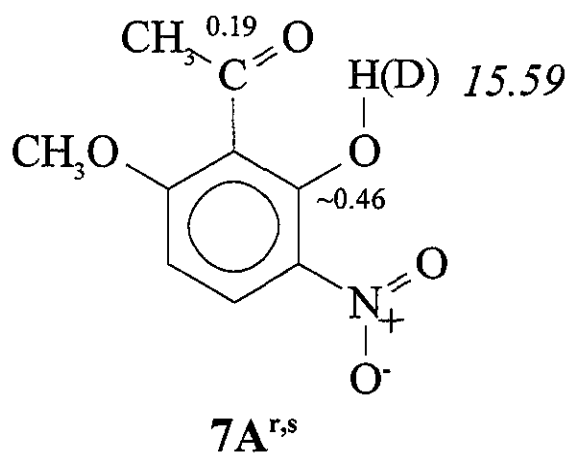
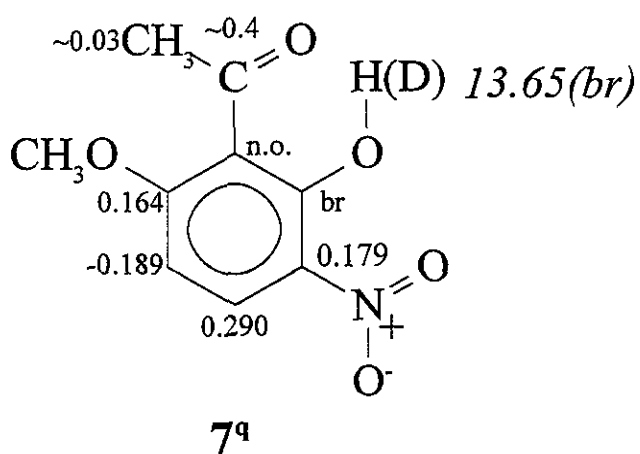
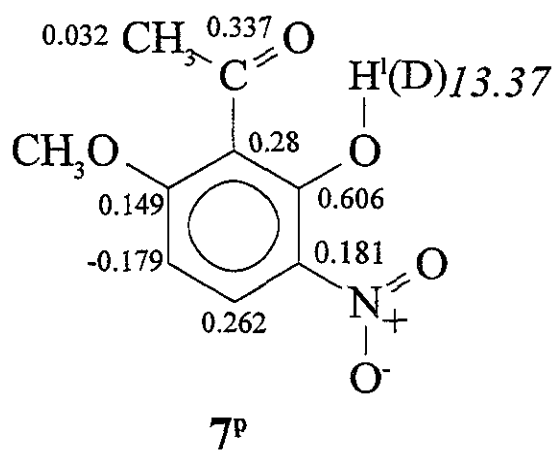
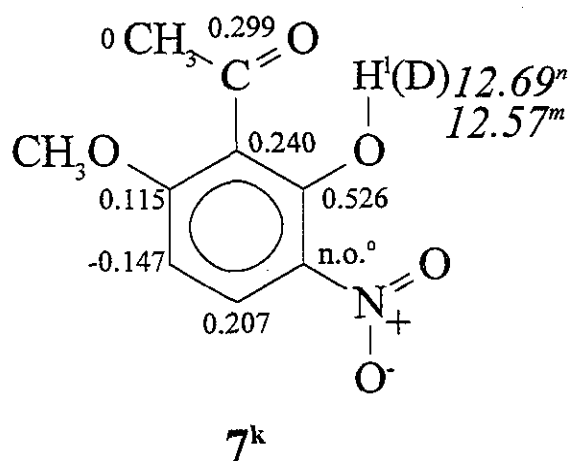
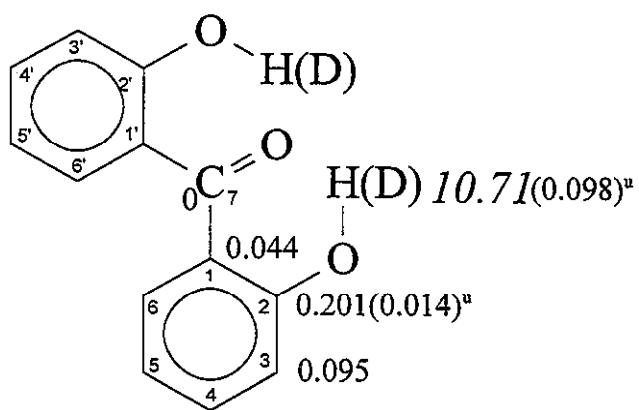


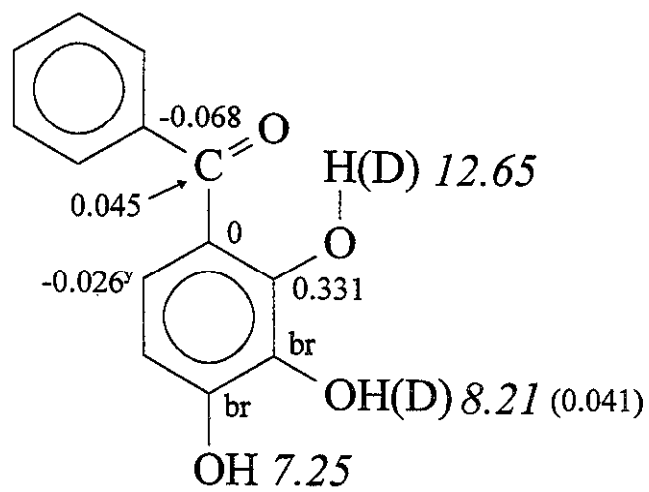
Fig. 3



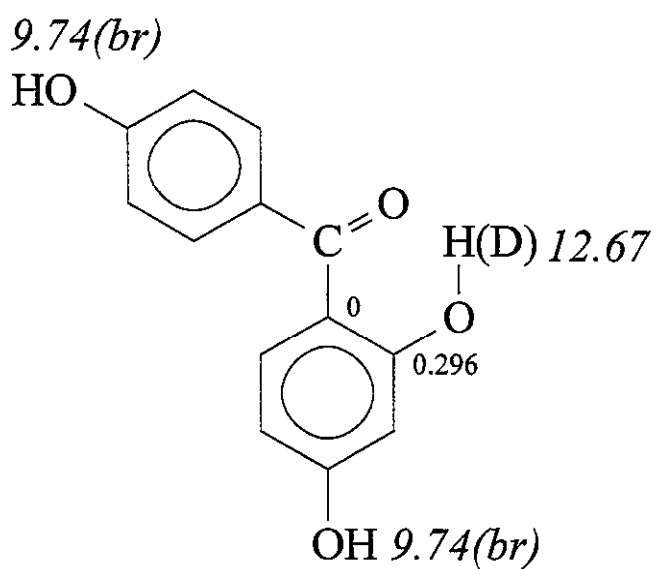




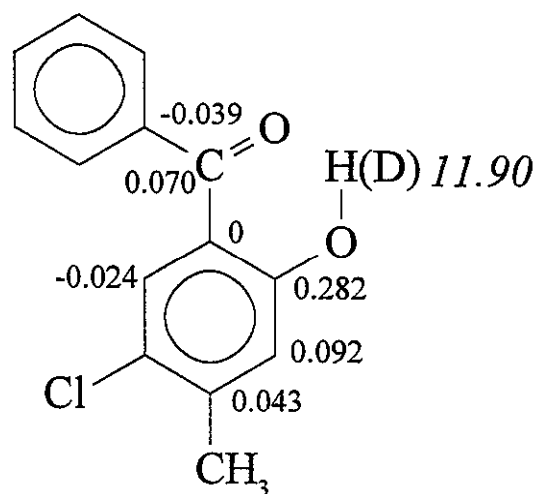
9^u



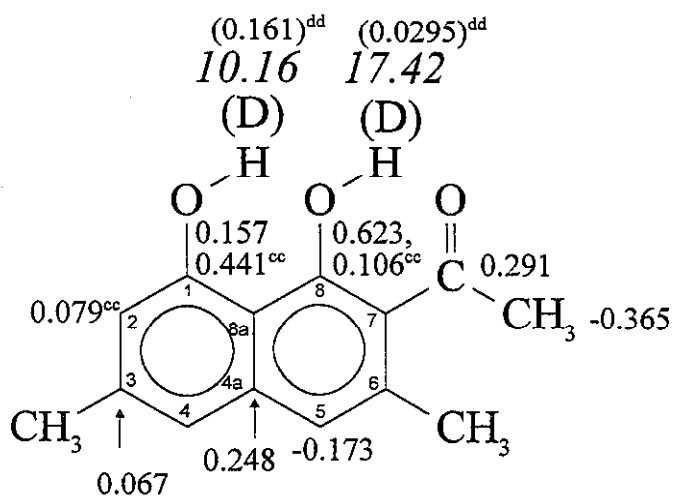
10^x



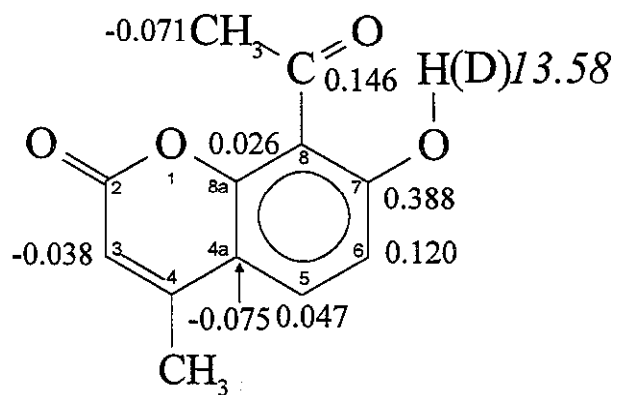
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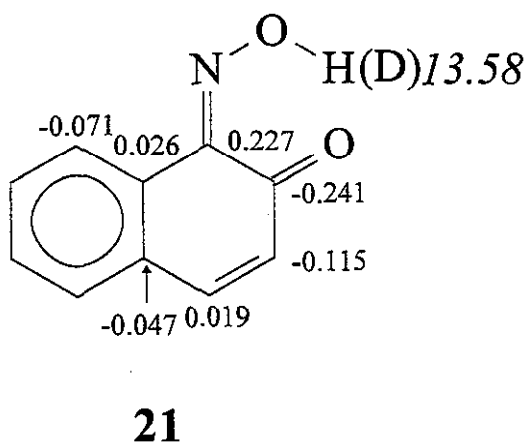
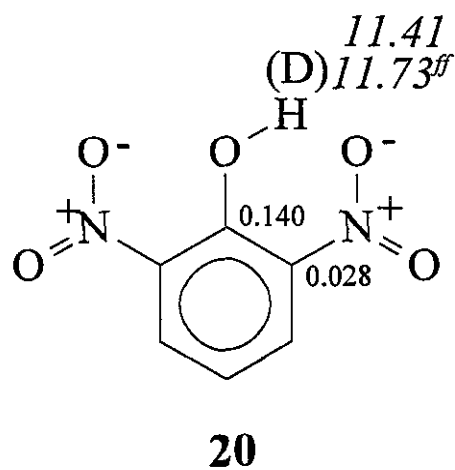
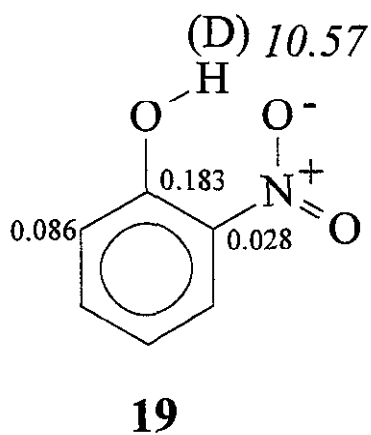
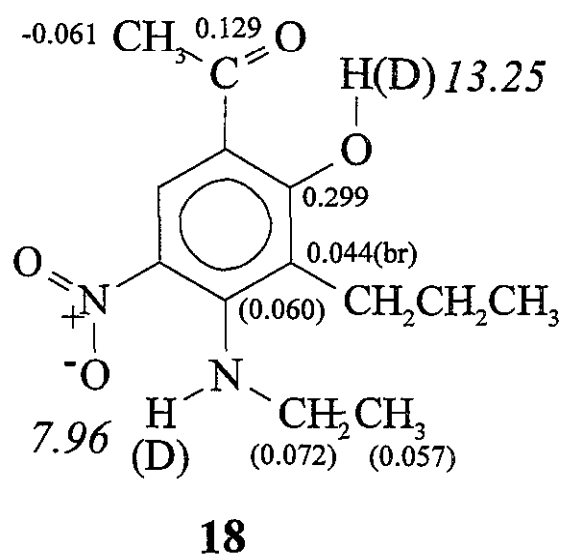
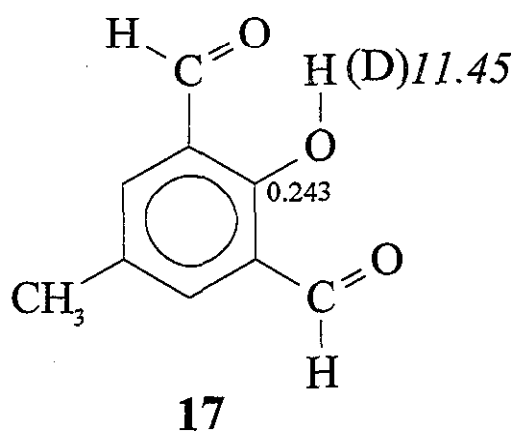
12



13^{bb}



14



Paper X

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Tautomerism of Enolic Triacetylmethane, 2-Acyl 1,3-cycloalkanediones, 5-Acyl Meldrums
Acids, and 5-Acyl 1,3-dimethylbarbituric Acids studied by means of Deuterium Isotope
Effects on ^{13}C Chemical Shifts

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Running Title: Determination of deuterium isotope effects on ^{13}C chemical shifts for enolic
Triacetylmethane, 2-Acyl 1,3-cycloalkanediones, 5-Acyl Meldrums Acids, and 5-Acyl 1,3-
dimethylbarbituric Acids.

Keywords: Deuterium isotope effects on chemical shifts, equilibrium isotope effects, variable
temperature NMR, tautomerism, Triacetylmethane, 2-Acyl 1,3-cycloalkanediones, 5-Acyl
Meldrums Acids, and 5-Acyl 1,3-dimethylbarbituric Acids

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ABSTRACT

Deuterium isotope effects on ^{13}C nuclear shielding, $^n\Delta\text{C}(\text{OD})$, were investigated for a series of enolic triacetylmethane, 2-acyl 1,3-cycloalkanediones, 5-acyl meldrums acids, and 5-acyl 1,3-dimethylbarbituric acids at different temperatures.

The enolic, 2-acyl 1,3-cycloalkanediones, 5-acyl meldrums acids, and 5-acyl 1,3-dimethylbarbituric acids, are all found to exhibit intramolecular enol-enol tautomerism. For the two former the equilibrium constants are estimated from the deuterium isotope effects on the enolic and carbonylic carbons. The equilibrium constants are estimated to 1.5 for the enolic 2-acyl 1,3-cyclohexanediones and 1.5 - 1.9 for 2-acetyl-1,3-cyclopentanedione favouring the form having endocyclic double bonds and to 0.8 for 5-acyl 1,3-dimethylbarbituric acids favouring the form having exocyclic double bonds. Apparently, the equilibrium position is unaffected by increasing the size of the acyl group, and therefore no distinct effects caused by sterical hindrance were observed.

The non-hydrogen bonded α -carbonyl group of the enolic triacetylmethane, 2-acyl 1,3-cycloalkanediones, 5-acyl meldrums acids, and 5-acyl 1,3-dimethylbarbituric acids cause a considerable high frequency shift of the OH ^1H chemical shifts. A plot of the latter vs. the sum of $^2\Delta\text{C}(\text{OD}) + ^4\Delta\text{C}(\text{OD})$ shows separate lines for five-membered ring enolic β -diketones and for open and six-membered ring enolic β -diketones, whereas data for the enolic triketones, enolic 5-acyl 1,3-dimethylbarbituric acids fall above these lines.

INTRODUCTION

2-acyl 1,3-cycloalkanediones,^{1,2} 5-acyl meldrums acids,^{3,4} and 5-acyl 1,3-dimethylbarbituric acids⁵ are only observed on the enolic form, whereas triacetylmethane, **7**, is reported to be on both the enolic and the keto forms.^{6,7}

The aim of this investigation is to determine whether enolic 2-acyl 1,3-cycloalkanediones, **1 - 6**, **8**, triacetylmethane **7**, 5-acyl meldrum's acids, **9 - 13**, and 5-acyl 1,3-dimethylbarbituric acids, **14 - 16**, are tautomeric. **1 - 8** are, earlier found to be tautomeric² (Fig. 1). Tautomerism is not immediately apparent in the NMR spectrum, as a weighted average of two potentially interchanging forms maybe observed. Deuterium isotope effects have been suggested for monitoring the existence of fast equilibria in carbocationic⁸ and tautomeric systems.⁹ Exchange of a hydrogen with deuterium perturbs the equilibrium, leading to equilibrium isotope effects, which are often large compared to the intrinsic isotope effects. The magnitude of the equilibrium isotope effect depends on two factors: (i) the difference of the nuclear shielding of the two equilibrating nuclei in question^{8,9} (ii) the change in the equilibrium constant, K_{eq} .^{8,9} The change in equilibrium constant depends on the position of the equilibrium.^{10,11}

The isotope effects are defined as $n\Delta C(D) = \delta C(H) - \delta C(D)$, where n is the number of bonds between the carbon in question and the deuterium. Large isotope effects on ^{13}C chemical shifts, $n\Delta C(OD)$, of both positive and negative signs are reported for tautomeric compounds.^{1,9,12-19} The sum of the isotope effect on the enolic and carbonylic carbons, $\Delta_{sum} = {}^2\Delta C(OD) + {}^4\Delta C(OD)$, is independent of the equilibrium contribution and the sum is shown to increase with increasing 1H OH chemical shifts^{11,20} and to be a possible indicator of tautomerism.

An interesting feature of the investigated compounds is the possibility to take part in tautomerism. Ester carbonyl groups are normally considered not having the ability to enolize. A comparable case is the 3,5-diacetyltetrahydropyran-2,4,6-trione,^{15,21} **17**, in which the carboxylic carbon involved in the tautomerism is part of the anhydride moiety.

Another important factor also related to tautomerism is the strength of the hydrogen bond. The 1H OH chemical shifts are shown to be correlated with the hydrogen bond strength.²² The two bond deuterium isotope effects on ^{13}C chemical shifts for intramolecularly

hydrogen bonded acyl aromatics can be correlated to the ^1H OH chemical shifts.^{23,24}

RESULTS

Chemical shifts

OH ^1H chemical shifts. The ^1H OH chemical shifts are presented in Scheme 1. The ^1H OH chemical shifts are shifted to higher frequency upon cooling, as seen from Scheme 1 and the negative temperature coefficients (Table 2).

Only enolic forms of **1 - 6** and **8 - 16** are observed in agreement with earlier reports.¹⁻⁵ For **7** both enolic and ketone forms were present at ambient temperature in CDCl_3 . However, the enolic form became more abundant upon cooling or on treatment with methanol.

For enolic 2-acyl 1,3-cyclohexandiones, **2 - 6** the ^1H OH chemical shifts are between $\delta = 18.10$ and $\delta = 18.37$ and for **1, 7** and **8** $\delta = 16.02$; $\delta = 17.22$ and $\delta = 14.87$ are found, respectively, in according to earlier findings.^{1,2,6,25} The OH resonances for **1** and **8** are exchange broadened at 300K, but became sharp at 250K and 200K, respectively. Earlier reports found $\delta = 16.50^1$ and $\delta = 15.60^2$ for **1**, in CDCl_3 and CCl_4 , respectively. This large variation found for the ^1H OH chemical shifts of **1**, must be due to intermolecular exchange or different solvent shielding capacities.

For **1** a coupling of 2.05 Hz at 190K was observed between the aldehyde proton and the OH proton, earlier reported as 1.9 Hz at 198K.²

For the enolic 2-acyl Meldrum acids, **9 - 13**, the enolic OH chemical shifts are found between $\delta = 15.07$ and $\delta = 15.60$. The OH resonances are broad at 300K showing that the OH protons have a tendency to exchange. The enolic 5-acyl 1,3-dimethylbarbituric acids, **14 - 16**, display ^1H OH chemical shifts between $\delta = 17.24$ and $\delta = 17.83$. The ^1H OH chemical shifts found here agree with the findings by Duus *et al.* ref. 3 - 5.

^{13}C chemical shifts. The ^{13}C NMR chemical shifts for **1 - 8** are given in Table 1. The ^{13}C NMR chemical shifts for **9 - 12, 13** and **14 - 16** are given in ref. 3, 4 and 5, respectively. The assignments of the ^{13}C chemical shifts were done by means of substituent effects, HETCOR²⁷ and COLOC²⁸ spectra and were compared when possible, with previously reported assignments. For **8** ^1H coupled ^{13}C spectrum showed a quartet centered at 198.3 ppm, which unambiguously assigned this resonance to carbon 6. From this spectrum the

assignment of the methyl carbon is also unambiguous.

The assignments of **1** and **3**, **9 - 12**, **13**, **14 - 16** agree with those of ref. **1**, **3**, **4** and **5**, respectively.

For compounds **1 - 8** the ^{13}C chemical shifts, of the enolic and carbonylic carbons display temperature variations comparable to those found for enolic β -diketones,¹¹ whereas **9 - 16** displays smaller temperature variations (Table 2).

^{17}O chemical shifts. ^{17}O chemical shifts are measured for **2**, **7** and **8**. The ^{17}O chemical shifts are found as $\delta^{17}\text{O-1} \sim 498$ ppm, $\delta^{17}\text{O-3} \sim 243$ ppm and $\delta^{17}\text{O-7} \sim 347$ ppm for **2**, $\delta^{17}\text{O-2}/^{17}\text{O-4} \sim 285$ ppm and $\delta^{17}\text{O-6} \sim 580$ ppm for **7**, $\delta^{17}\text{O-1} \sim 469$ ppm, $\delta^{17}\text{O-3} \sim 215$ ppm and $\delta^{17}\text{O-6} \sim 374$ ppm for **8**.

Isotope effects

The deuterium isotope effects on ^{13}C chemical shifts are given in Scheme 1. For **2** the isotope effects of C-3, C-4, C-7, C-8 and the sum of $\Delta\text{C-3(OD)}$ and $\Delta\text{C-7(OD)}$ are given in Figure 2 as a function of temperature. The significant temperature variations seen for **2** are also observed for **1**, **3 - 8**. Compounds **9** and **11** show a decreasing isotope effect on both the carbonylic C-6 and the enolic C-7 with decreasing temperature. For **9** a temperature dependence of the deuterium isotope effects is also observed on C-2, but not on C-8. For **9** and **11**, the temperature variations are only one tenth of those observed for **1 - 8**, (Table 2). An increase in the isotope effects is observed for C-8, the enolic C-7 and the carbonylic C-6 as a function of decreasing temperature for the enolic 5-acyl 1,3-dimethylbarbituric acids **14 - 16**. The isotope effect on C-5 decreases with decreasing temperature. The temperature variations on the deuterium isotope effects for **14 - 16** is in the region between those observed for **1 - 8** and **9 - 13**.

The isotope effects on the ^{13}C chemical shielding are large for all the studied compounds and the effects are observed throughout the system. For **9 - 16** unusual isotope effects are observed on C-2. C-2 is positioned after the ester oxygen or the amide nitrogen for meldrum- and barbituric acids, respectively.

The OH proton show tendency to intermolecular exchange for **1**, **8** and **10 - 13** and

therefore isotope effects are not observed at 300K. For **8** the isotope effects were only observed when the sample was cooled to 190K. This was also seen for 2-acyl 1,3-indandiones.^{1,16}

The isotope effects for **1 - 8** on C-4 (C-1/C-5 for **7**) and the enolic carbon C-3 (C-2\C-4 for **7**) increase as a function of decreasing temperature. For C-8 and the carbonylic carbon C-7 a decrease in the deuterium isotope effects was observed as a function of decreasing temperature for **2 - 6**.

For the C-9 methyl carbon of **15** isotope effects of -0.120 and -0.194 ppm are observed at 300K and 200K, respectively. This is a large four bond isotope effect compared to e.g. 2-propionyl-1,3-indandione.¹⁶

$\Delta H(OD)$

A deuterium isotope effect of 0.045 ppm on the aldehyde proton, is observed for **1** at 170K - 220K, (Scheme 1).

For **2**, an isotope effect on the methyl protons, with a magnitude of 0.007 ppm, is observed in the temperature region 200K - 300K, (Scheme 1).

DISCUSSION

OH 1H chemical shift

The 1H OH chemical shifts for the studied compounds resonate at high frequency indicating strong intramolecular hydrogen bonding.²² When lowering the temperature the 1H OH chemical shift moves to higher frequency.

A 1H OH chemical shift of 14.87 is observed for **8**, **8** being a five-membered ring system. This value is significantly smaller compared to the values for the six-membered and open system **2 - 7**. This is due to the less favourable hydrogen bonding geometry in the five-membered ring system. The 1H OH chemical shifts found for **1 - 8** are at significantly higher frequency than for the corresponding enolic β -diketones,^{11,19,29,30} without a carbonyl group in the α -position. The difference is of the order of 2-3 ppm, which indicate that the α -carbonyl

group contributes to the resonance, as shown in forms C and D in Figure 3. A similar high frequency ^1H OH chemical shift is also seen for other enolic β -diketones with a carbonyl in α -position.^{2,30} **9** - **13** are esters and should therefore be compared with enolic β -keto esters like ethyl acetoacetate (^1H OH chemical shift of 12.11 ppm).³¹ The difference of ca. ~ 3 ppm between the ^1H OH chemical shift of enolic 5-acyl meldrum's acids and those of the enolic β -keto esters can be explained by the contributions of forms C and D in Figure 3.

^{13}C chemical shifts

The two carbonyl carbons and the enolic carbon, for each compound **1** - **8** are all observed above 195 ppm, except the aldehyde **1**. These high frequency chemical shifts are partly explained by the intramolecular enol-enol tautomeric equilibrium.² The C-3 and C-7 chemical shift for **2**, (198.7 ppm and 203.0 ppm, respectively) are seen to be deshielded, when compared to the carbonylic/enolic carbon chemical shifts of acetylacetone (191.2 ppm).^{1,11} It is well known that in the $\text{O}=\text{C}-\text{C}=\text{C}$ fragment, the β -carbon is shifted to high frequency.³² The C-3 enolic form for **2** is dominating (see later), which explains the high frequency resonance of C-7. Therefore, the chemical shift of C-3 is expected to be lower than that of acetylacetone, found at 191.14 ppm.¹¹ This implies that the resonance form C in Figure 3 is contributing. To extend this comparison further, the C-2 and C-4 chemical shifts of **7** are at 192.6 ppm, which is much lower than the chemical shifts of **2** (Table 1). For **7** the chemical shift of C-6 is at 200.4 ppm compared to that of 195.3 ppm for C-1 of **2** indicating that the acetyl group of **7** is less strongly conjugated than the carbonyl group of **2**.

^{17}O chemical shift

The ^{17}O chemical shifts for **7** show that the resonance for the $\alpha\text{-CH}_3\text{C}=\text{O}$ group (580 ppm) is very close to the value found for simple methyl alkyl ketones.³³ The averaged chemical shift of the enolized ^{17}O -2 and ^{17}O -4 at 285 ppm is at slightly higher frequency than for enolic β -diketones.¹¹

For **2** and **8** the picture is different. The resonances of the oxygen at C-1 are now at 498 ppm for **2** and at 469 ppm for **8**, both considerably to lower frequency than oxygens of

the C=O groups of cyclohexanone and cyclopentanone.³⁴ For **8** ^{17}O -6 is at higher frequency than ^{17}O -7 for **2** and ^{17}O -3 is to lower frequency for **8** then for **2**, which support that **8** is more on form A (Figure 3) than **2** (see later). The sum of ^{17}O -3 and ^{17}O -7 for **2** is ~590 ppm and for the **8** the sum of ^{17}O -3 and ^{17}O -6 is ~589 ppm, which is a high frequency shift of 60 - 70 ppm, compared to the sum found for 2-acetylcyclohexanone and 2-acetylcyclopentanone.³⁵ These results support the conclusions reached previously: i) the $\alpha\text{-CH}_3\text{CO}$ group of **7** is not conjugated to any large extent to the rest of the molecule and ii) the =CHOH oxygen is shifted considerably to higher frequency compared to β -diketones¹¹ again underlining the positive charge at oxygen. This high frequency shifts shows that the use of standard values as presented by Gorodetsky *et al.*³⁵ is only valid for a group of very similar compounds.

Isotope effects

The large isotope effects on C-1, C-4, C-8, the enolic C-3 and the carbonylic C-7 for **1** - **6**, (Scheme 1), leave little doubt that these compounds are tautomeric, in agreement with earlier findings.² The isotope effects at C-3 and C-7 consist of intrinsic and to a large extent equilibrium contributions. Upon deuteration the equilibrium is shifted. Assuming that the acetylic carbonyl carbon chemical shift is to higher frequency than the corresponding enolic carbon atom chemical shift and that for carbon 3 the carbonyl carbon chemical shift is to higher frequency than the enolic carbon chemical shift. Then the relative small isotope effect at C-7 and the large positive isotope effect at C-3 tell that the equilibrium is shifted in the direction of the tautomer shown in Scheme 1. This is most likely also the dominant tautomer, as the equilibrium upon deuteration normally leads to more of the most stable tautomer,^{11,15} this is supported by the large isotope effects found on C-3. This finding is corroborated by the ^{13}C chemical shifts (see previously).

Only small changes are observed in the isotope effects, when changing the acyl group from acetyl, **2** and **3** to pivaloyl, **6**, which indicates that no sterical hindrance is observed, though this might have been expected³⁶ (see later).

The five-membered ring structure offers a less favourable hydrogen bond, and therefore smaller isotope effects can be expected, for **8** compared to **2**. From the isotope effect on C-3 it is clear that the C-3 enolic form, (see Figure 3 A), is dominating (see above). This is

unusual, since the five-membered ring system normally prefers the tautomer with the exocyclic double bond.^{11,29} Compound **8** is seen to be tautomeric from a comparison of the isotope effects on the enolic C-3 and the carbonylic C-6 carbons, (Scheme 1), with the isotope effects on the enolic and carbonylic carbons for the tautomeric 2-acetylcyclopentanone (0.949 ppm and -0.0125 ppm respectively).¹¹ This is further supported by the large isotope effects on C-4 and the large negative value found for C-7 and in agreement with earlier reports.²

The isotope effects on C-7 for **9** - **13**, show that this carbon is enolic (form B in Figure 3). To establish tautomerism for **9** - **13** is not trivial. If the isotope effects were to be interpreted as if **9** - **13** were non-tautomeric, we will have a $^2\Delta\text{C-7(OD)}$ value of ~ 0.6 ppm, which is a large two bond isotope effect, and not observed in esters only for ketones.^{1,16} The isotope effect on C-3 will then be a four-bond isotope effect, and a four-bond isotope of 0.4 - 0.5 ppm has never been observed in non-tautomeric systems. The isotope effects on C-2 observed for **9**, **10** and **11** are also very unusual, due to the ester oxygen between the site of exchange and the carbon in question. The isotope effect on C-2 is in a non-tautomeric system, a six-bond effect of the order of ~ -0.1 ppm, not seen for esters. If **9** - **13** were non-tautomeric and on the C-7 enolic form, we would expect, based on isotope effect measurements of the enol form of β -ketoesters,^{11,13} the following intrinsic isotope effects: C-7 ~ 0.4 ppm, C-6 ~ 0.1 ppm and C-8 ~ 0.1 ppm and little else. If it were on the C-6 enolic form, the large isotope effect would be on C-6. The observed isotope effects of **9** - **13** do not fit to this picture most likely because a tautomeric equilibrium is at hand.

The temperature dependence on the isotope effects for **9** and **11** decrease with decreasing temperature for both C-6 and C-7, (Table 2), this is unusual because normally they will be of opposite signs. It is seen that both isotope effects at C-6 and C-7 are larger than their intrinsic contributions, meaning that both equilibrium contributions are positive. This is unusual, but can be explained, as seen below, if the chemical shift of both nuclei is to higher frequency in one tautomer than in the other. For **9** the isotope effects and the changes in chemical shifts with temperature both support that the structure shown in Scheme 1 is the dominant. Assuming that $\delta\text{CH}_3\text{CO} > \delta\text{CH}_3\text{COH}$ and that $\delta=\text{COR} > \delta\text{COOR}$ the change in chemical shifts will be positive upon lowering of the temperature. Upon deuteration the equilibrium contribution for both C-6 and C-7 will be positive and of approximately the same

magnitude judging from the changes observed with changing the temperature (Table 2). C-6 will have a small intrinsic contribution as the C-6 enolic form is only slightly populated. C-7 will have a relative small intrinsic contribution as $^2\Delta\text{C}(\text{OD})$ for an enolic β -ketoester is ~ 0.4 ppm.^{11,13} A rough estimate suggests that the form of Scheme 1 contribute 80%.

The isotope effect on C-7 for **14** - **16** shows that C-7 are on the enolic form, (form B Figure 3). The large isotope effects on C-5, C-8, the carbonylic C-6 and the enolic C-7 clearly demonstrate that the 2-acyl 1,3-dimethylbarbituric acids are tautomeric. For **15** an isotope effect of -0.12 ppm at 300K and -0.194 ppm at 200K are observed at C-9. Such effects are not observed in an aliphatic moiety four-bond away from the site of exchange unless the system is tautomeric (see 4).¹¹ The isotope effect on C-2 is unusual due to the amide nitrogen between the site of exchange and the carbon in question. This type of effect is only observed in tautomeric system.¹⁵ The temperature dependence on the isotope effects for **14** - **16** are negative for both C-6 and C-7, (Table 2), which was also observed for the enol form of β -ketoamides.¹⁴

Δ_{sum}

Δ_{sum} is equal to $\Delta\text{C-3} + \Delta\text{C-7}$ for **1** - **6**, $\Delta\text{C-2} + \Delta\text{C-4}$ for **7**, $\Delta\text{C-3} + \Delta\text{C-6}$ for **8** and $\Delta\text{C-6} + \Delta\text{C-7}$ for **9** - **16**. The OH ^1H chemical shifts increases as the sum of the observed two- and four- bond isotope effect increase Figure 4. Different types of compounds are found to have different slopes (Figure 4). The tautomeric compounds are seen to have a less steeper slope compared to the non-tautomeric, except for 2-acyl 1,3-indandiones which are considered non-tautomeric.^{1,16}

A rule of thumb state for ketones that if the sum of the isotope effect on the enolic and carbonylic carbons, Δ_{sum} , are above 1.2 ppm for a six-membered ring system and above 0.8 ppm for a five-membered ring system, the systems are tautomeric.¹¹ Δ_{sum} for **2** - **6**, **8** and **14** - **16** are above 1.2 ppm and for **8** above 0.8 ppm, which again support that these compounds are tautomeric.

The Δ_{sum} values for **9** - **13** are between 0.970 - 1.199 ppm. The carbonylic carbon of **9** - **13** are part of an ester moiety and esters normally displays smaller isotope effects than ketones.^{11,23,37,38} For the tautomeric 3,5-diacetyltetrahydropyran-2,4,6-trione, (**17**), the sum is

0.965.¹⁵

Equilibrium constant, K_{eq}

The equilibrium constant describing the intramolecular enol-enol interconversion is $K_{eq} = [A]/[B] = X/(1-X)$, [A] and [B] being the concentrations of forms A and B in Figure 1.

We have earlier reported¹¹ the isotope effects on the enolic and carbonylic carbons for enolic β -diketone as a function of the molar fraction, X. The part for $X = 0 - 0.5$ is based on five-membered ring systems, the part for $X = 0.5 - 1$ on six-membered ring systems. For the five-membered ring system the picture between $X = 0.5 - 1.0$ is expected to be a reflection around $X = 0.5$ of $X = 0 - 0.5$. For the six-membered system a reflection around $X = 0.5$ of $X = 0.5 - 1.0$ is expected for $X = 0 - 0.5$. This gives the function shown in Figure 5, where the solid line is the polynomial fit to the data and the dotted lines are the reflected part. The isotope effects on the enolic and carbonylic carbons give two fix points and the mole fraction can directly be read.

The mole fractions were found to 0.58-0.60 for **2 - 6** and to 0.60-0.65 for **8**. **7** is symmetric. The mole fraction for **1** is determined to 0.65-0.70 and to 0.45 for **14 - 16**. The model is based on enolic β -diketone and **1** being an aldehyde and **14 - 16** being amides make the determination of the mole fractions tentative.

The mole fractions for **9 - 13** cannot be determined by this method due to the smaller isotope effect observed for the esters.

OH ^1H chemical shifts vs. sum of isotope effects. Two conspicuous results are seen from Figure 4. One is that data for enolic β -dicarbonyl compounds falling in two different levels, one for five-membered rings and one for open and six-membered rings. The second feature is that the data for the enolic forms of the enolic triketones and 5-acyl 1,3-dimethylbarbituric acids fall above these lines. This feature is very apparent for usnic acid and its derivatives,²³ but also clearly seen for data of **2 - 8** and for **13 - 16**. On the other hand, **9 - 13** show no distinct effects. For five-membered rings, the 2-acyl 1,3-indandiones^{1,16} show the effect of the extra carbonyl group. The high frequency position of the OH proton resonance and the length of the O-H bond of the enolic β -triketones are related to the importance of the C form of

Figure 3. This will also lead to a higher acidity of the OH proton as evidenced by the intermolecular exchange that requires cooling for observation of sharp OH resonances of compounds **1**, **8** and **10 - 13**. A question that can be asked is as follows: "Does this lengthening of the OH bond also lead to a strengthening of the hydrogen bond?".

From the dotted guide line in figure 4, the slope for the aromatic compounds seems steeper than the slope for the enolic β -diketone compounds.

CONCLUSIONS

The enolic 2-acyl 1,3-cycloalkanediones, 5-acyl meldrum's and 5-acyl 1,3-dimethylbarbituric acids, are found tautomeric by means of isotope effect on ^{13}C nuclear shielding. The equilibrium constants are estimated from the deuterium isotope effects on the enolic and carbonylic carbons. The equilibrium constants are found to be 1.50 for the enolic 2-acyl 1,3-cyclohexanediones and 1.5 - 1.9 for 2-acetyl-1,3-cyclopentanedione in favour of the endocyclic double bonded form. For 5-acyl 1,3-dimethylbarbituric acids an equilibrium constant of 0.80 is found in favour of the exocyclic double bond form. The equilibrium position is not must affected by varying the acyl group.

Effects on isotope effects due to sterical hindrance were not observed for 2-pivaloyl-1,3-cyclohexanedione compared to 2-acetyl, 2-propionyl- and 2-isobutyryl-1,3-cyclohexanedione. The ^{13}C and ^1H chemical shifts show that the resonance forms in which the C-1 carbonyl participate, forms C and D (Figure 3), are important.

EXPERIMENTAL

Compounds

2-acetyl-1,3-cyclohexanedione, **2**, triacetylmethane, **7** and 2-acetyl-1,3-cyclopentanedione, **8**, 3,5-diacetyltetrahydropyran-2,4,6-trione, **17** were purchased from Aldrich. 2-Formyl-4,4-dimethyl-1,3-cyclohexanedione, **1**, 2-propionyl-4,4-dimethyl-1,3-cyclohexanedione, **4**, and 2-isobutyryl-4,4-dimethyl-1,3-cyclohexanedione, **5** were prepared according to ref. 40. 2-Acetyl-4,4-dimethyl-1,3-cyclohexanedione, **3** and 2-pivaloyl-4,4-dimethyl-1,3-cyclohexanedione, **6** were prepared in an analogy to **4** using anhydrous sodium acetate/acetic anhydride and anhydrous sodium pivalate/pivalic anhydride, instead of anhydrous sodium propionate/propionic anhydride.

5-(1-hydroxyethylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane, **9**, 5-(1-hydroxypropylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane, **10**, 5-(1-hydroxy-2-methyl-propylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane, **11**, 5-(1-hydroxy-2-phenyl-ethylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane, **12**, 5-(1-hydroxy-4-nitro-benzylidene)-2,2-dimethyl-4,6-dioxo-1,3-dioxane, **13**, 5-

(1-hydroxyethylidene)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane, **14**, 5-(1-hydroxypropyliden)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane, **15** and 5-(1-hydroxy-2-methyl-propyliden)-1,3-dimethyl-2,4,6-trioxo-1,3-diazane, **16** were prepared as described in reference 3 - 5.

NMR experiments

The ^{13}C NMR spectra were recorded in CD_2Cl_2 or CDCl_3 on a Bruker AC 250 NMR spectrometer at 62.89 MHz with a digital resolution of 0.55 Hz per point. Spectra of samples with different degree of deuterium incorporation were measured to determine the signs of the isotope effects. The ^{13}C chemical shifts were measured relative to internal TMS at 0.5 M in CDCl_3 at 300K and in CD_2Cl_2 at 170- 230K with a digital resolution of 1.1 Hz per point. The ^{17}O chemical shifts (natural abundance) were measured relative to external H_2^{17}O at 3 M in CDCl_3 at 300K, with a digital resolution of 34.9 Hz per point at 33.908 MHz. Typically 2×10^5 - 6×10^5 scans were accumulated.

HETCOR²⁷ and COLOC²⁸ spectra were recorded as described in Ref. 38.

Deuteration of compounds

100 mg of liquid compounds were dissolved in 1 ml CD_2Cl_2 and stirred with 0.5 ml $\text{D}_2\text{O}/\text{H}_2\text{O}$, usually overnight. The $\text{D}_2\text{O}/\text{H}_2\text{O}$ phase was removed and the remaining organic phase was dried over anhydrous Na_2SO_4 . Crystalline compounds were dissolved in MeOD/MeOH and evaporated. The degree of deuteration was varied by varying the MeOD/MeOH or $\text{D}_2\text{O}/\text{H}_2\text{O}$ ratios, and it was estimated from the ^1H NMR spectra.

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Legends to Figures and Schemes

Scheme 1.

Deuterium isotope effects on ^{13}C chemical shifts in ppm. The dominant tautomer in CDCl_3 or CD_2Cl_2 at 300 K is shown, if nothing else is stated. ^1H OH chemical shifts are given in italic. Data for compound 17 is taken from ref. 15. Notice the arrows are incorrectly position in ref. 15.

Hydrogen bonds (see Fig. 1) are not included for reasons of clarity.

a. 250 K, b. 200 K, c. isotope effect on ^1H , d. 300 K, e. 220 K, f. 230 K, g. 260 K, h. 190 K, i. 170 K.

Figure 1.

Tautomerism of enolic 2-acyl 1,3-cycloalkandiones ($\text{Y}=\text{C}$), 5-acyl barbituric acids ($\text{Y}=\text{N}$) and 5-acyl meldrum acid ($\text{Y}=\text{O}$).

Figure 2.

Deuterium isotope effects on ^{13}C chemical shifts for 2 as a function of temperature. The sum is that of $\Delta\text{C-3(OD)} + \Delta\text{C-7(OD)}$.

Figure 3.

Resonance forms of 2-acyl 1,3-cycloalkandiones, ($\text{Y}=\text{C}$), 5-acyl meldrum acid, ($\text{Y}=\text{O}$), and 5-acyl barbituric acid, ($\text{Y}=\text{N}$).

Figure 4.

The OH ^1H chemical shifts (in ppm) as function of the sum of the isotope effects on the enolic (or hydroxy for non-tautomeric compounds) carbon and the carbonylic carbon. Open symbols indicate compounds which are considered non-tautomeric and solid symbols indicate compounds which are considered tautomeric.

□ 2-hydroxy-acyl aromatic compounds ref. 23, ▲ open and 6-membered ring enolic β -diketones from ref. 11 and 13, the solid line is a guide line, ▼ enolic 5-membered ring β -diketones from ref. 11, the solid line is a guide line, Δ enolic 2-acyl 1,3-indandione ref. 1 and

16, ■ usnic acid and derivatives of usnic acid from ref. 13, ♦ enolic ethyl 2-acetyl-3-oxo-butyrate from ref. 39, ▽ enolic five-membered ring β -diketones, X is compound 1 - 8, 14 - 16 and * is compound 9 - 13.

The dotted lines are guide lines for the slope, for aromatic and enolic β -diketones compounds.

Figure 5.

Observed isotope effects on the enolic and carbonylic carbon as a function of the mole fraction X. The solid line is a 4-order polynomial fit to the observed data from ref. 11. The dotted line is reflection of the solid line around $X = 0.5$.

Table 1. ^{13}C chemical shifts (ppm) of compound **1** - **8**, obtained at 300K, 0.5M in CDCl_3 and at low temperature in CD_2Cl_2 .

Compounds	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
1	195.1	113.4	195.1	45.4	50.9	32.0	190.9	-	-	28.4	28.4
	196.0 ^a	112.9 ^a	194.9 ^a	44.4 ^a	50.4 ^a	32.3 ^a	192.6 ^a	-	-	28.3 ^{a,b}	28.3 ^{a,b}
2	195.3	113.5	198.7	33.3	19.1	38.6	203.0	28.7	-	-	-
	196.3 ^c	113.1 ^c	199.2 ^c	33.0 ^c	18.8 ^c	38.5 ^c	203.8 ^c	30.4 ^c	-	-	-
3	195.0	112.5	198.0	46.9	52.5	30.7	202.6	28.4	-	28.0	28.0
	195.5 ^d	112.3 ^d	198.3 ^d	46.3 ^d	52.2 ^d	30.9 ^d	203.2 ^d	29.4 ^d	-	28.0 ^d	28.0 ^d
4	195.0	111.8	197.1	46.6	52.5	30.6	206.3	34.0	8.3	28.1	28.1
	195.4 ^e	111.4 ^e	196.9 ^e	45.8 ^e	52.0 ^e	30.6 ^e	206.5 ^e	34.4 ^e	7.7 ^e	27.8 ^e	27.8 ^e
5	194.8	111.0	198.6	47.0	52.9	30.5	209.8	36.0	18.7	28.1	28.1
	195.2 ^e	110.4 ^e	198.5 ^e	46.4 ^e	52.3 ^e	30.5 ^e	209.9 ^e	36.0 ^e	18.5 ^e	27.9 ^e	27.9 ^e
6	195.1	113.2	197.8	47.0	52.8	30.4	204.5	48.6	28.1	28.2	28.2
	195.7 ^e	112.8 ^e	198.3 ^e	46.6 ^e	52.5 ^e	30.6 ^e	204.8 ^e	48.1 ^e	28.0 ^e	28.2 ^e	28.2 ^e
7	24.3	192.6	119.0	192.6	24.3	200.4	31.9	-	-	-	-
	25.5 ^e	193.8 ^e	118.8 ^e	193.8 ^e	25.5 ^e	201.7 ^e	33.0 ^e	-	-	-	-
8	199.9	114.6	203.6	28.4	33.7	198.3	25.8	-	-	-	-
	201.5 ^f	115.2 ^f	203.5 ^f	28.2 ^f	33.9 ^f	200.0 ^f	27.6 ^f	-	-	-	-

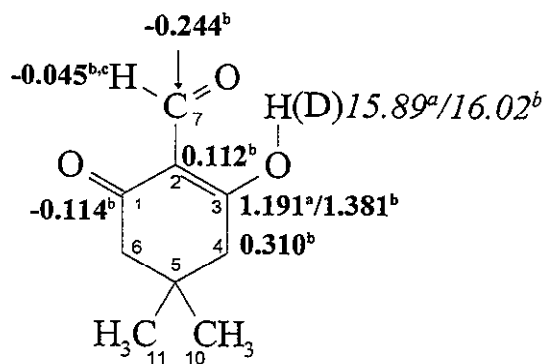
For assignment of carbon atoms, see scheme 1.

a: 200K; b: broad; c: 210K; d: 220K; e: 230K; f: 190K.

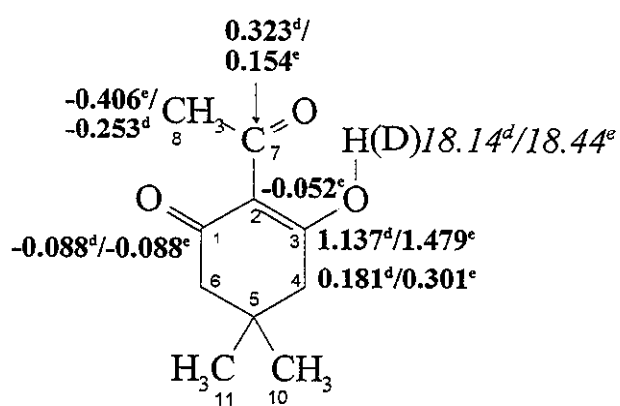
Table 2. Temperature variation on O¹H and on the deuterium isotope effect on ¹³C chemical shift. The sum of two- and the four-bond deuterium isotope effects on ¹³C chemical shift, Δ_{sum} .

Compounds	$\Delta_{\text{temp}}\delta\text{OH}^{\text{a}}$	$\Delta_{\text{temp}}\Delta\text{C}^{\text{a}}_{\text{enolic}}^{\text{h}}$	$\Delta_{\text{temp}}\Delta\text{C}^{\text{a}}_{\text{carbonylic}}^{\text{h}}$	$\Delta_{\text{sum}}^{\text{o}}$	$\Delta_{\text{sum}}^{\text{n}}$
1	-2.60 ^b	-3.80 ^b	-	1.137 ^c	-
2	-5.63 ^d	-4.10 ^d	2.29 ^d	1.564 ^e	1.419
3	-3.75 ^d	-4.28 ^d	2.11 ^d	1.633 ^e	1.460
4	-4.57 ^f	-4.10 ^f	2.09 ^f	1.628 ^g	1.487
5	-6.00 ^f	-3.20 ^f	1.54 ^f	1.574 ^g	1.460
6	-5.71 ^f	-2.97 ^f	0.87 ^f	1.633 ^g	1.486
7	-1.43 ^f	-2.40 ^f	-2.40 ^f	2.288 ^g	1.952
8	-	-6.70 ⁱ	j	1.005 ^k	-
9	0.00 ^l	0.35 ^l	-0.39 ^l	0.970 ^m	1.044
11	-0.86 ^f	-	-0.46 ^f	1.041 ^g	-
10	-	-	-	1.015 ^g	-
12	-	-	-	1.084 ^g	-
13	-	-	-	1.199 ^e	-
14	-1.60 ^l	-0.93 ^l	-0.24 ^l	1.509 ^m	1.393
15	-2.70 ^l	-1.59 ^l	-0.017 ^l	1.543 ^m	1.401
16	-1.10 ^l	-1.53 ^l	-0.23 ^l	1.590 ^m	1.414

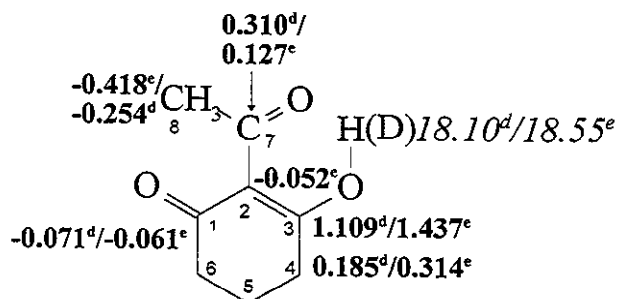
a: 10⁻³ ppm/K; b: 200K - 300K; c: 200K; d: 200K - 300K; e: 220K; f: 230K - 300K; g: 230K; h: enolic and carbonylic refer to the carbon most on the enolic and carbonylic form respectively i: 170K - 190K; j: no isotope effect is observed at 190K; k: 170K; l: 200K - 300K; m: 200K; n: 300K; o: at low temperature.



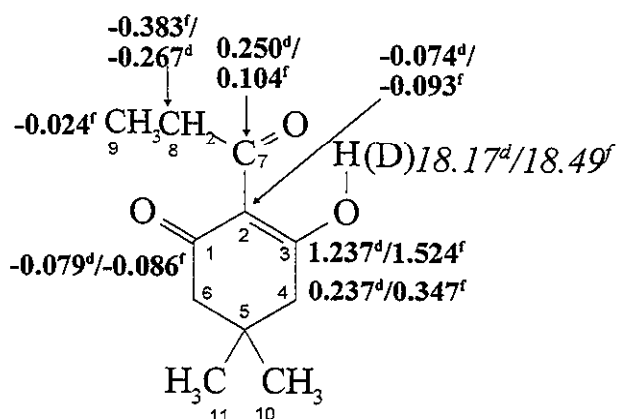
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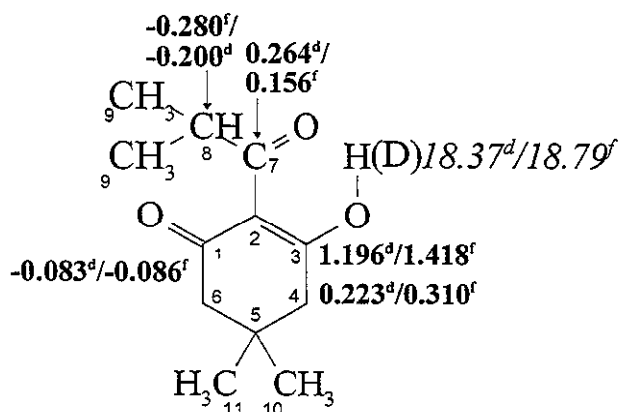
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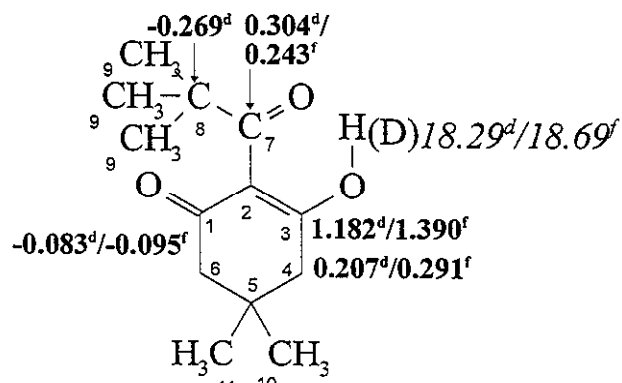
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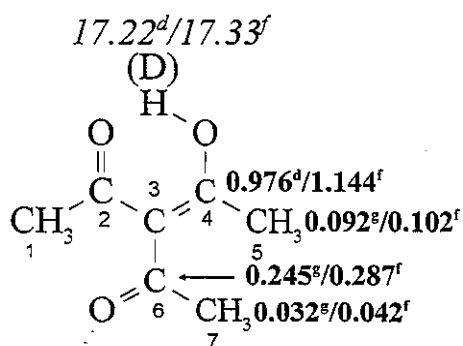
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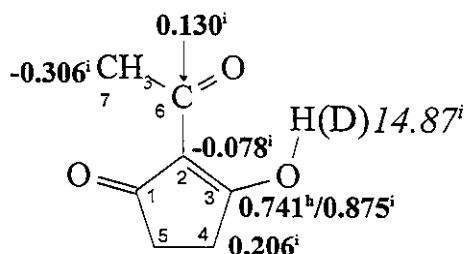
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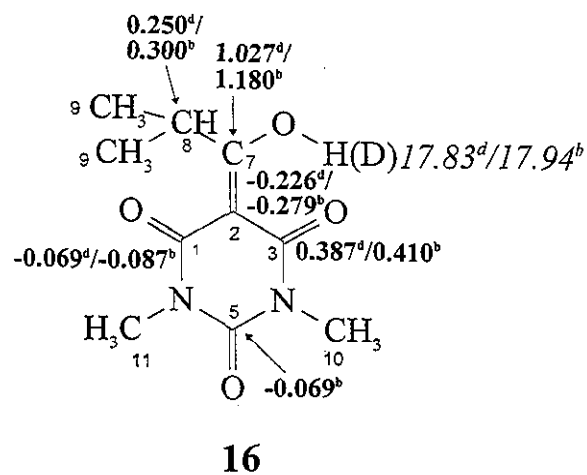
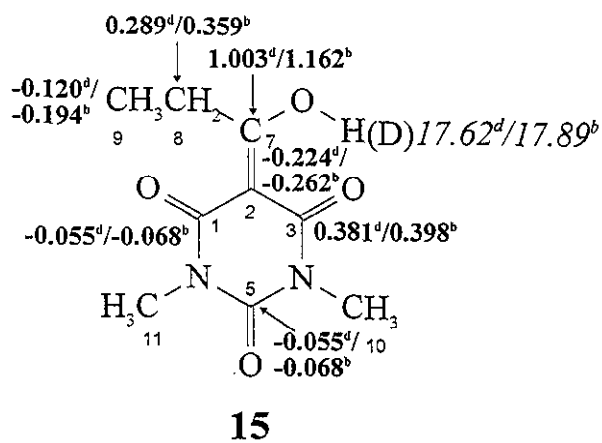
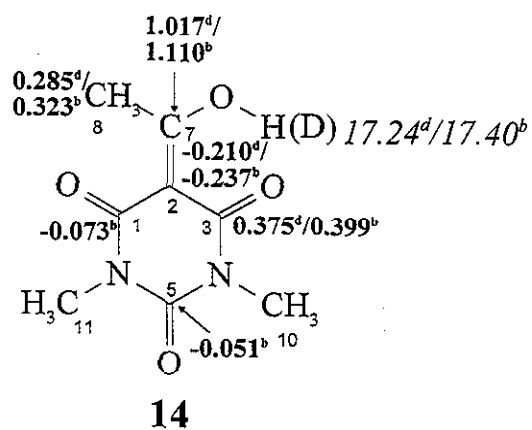
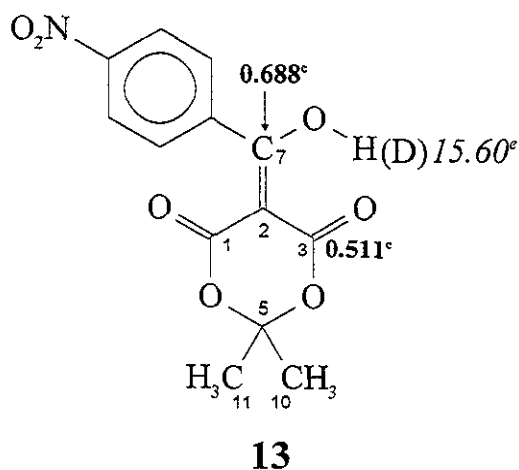
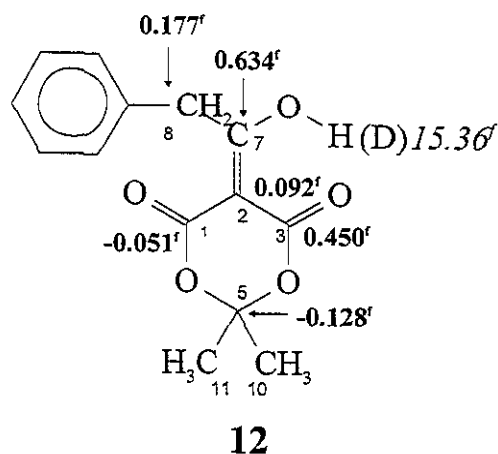
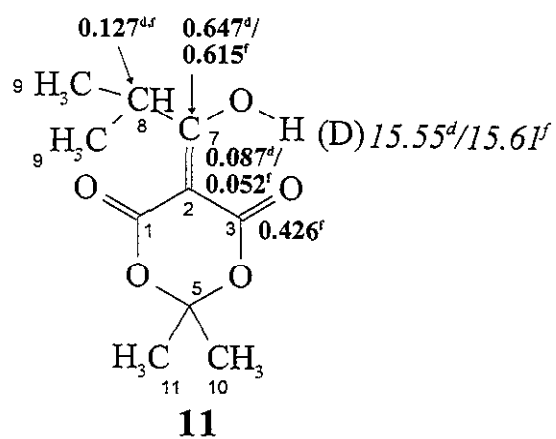
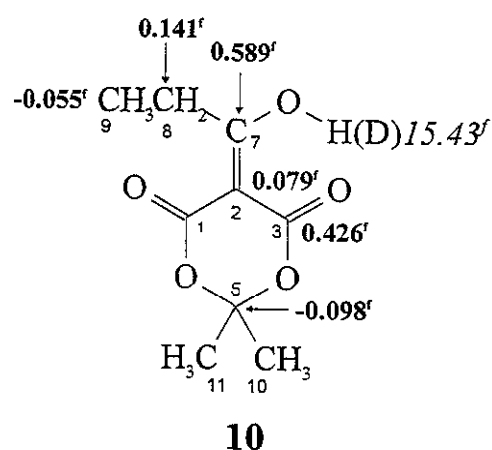
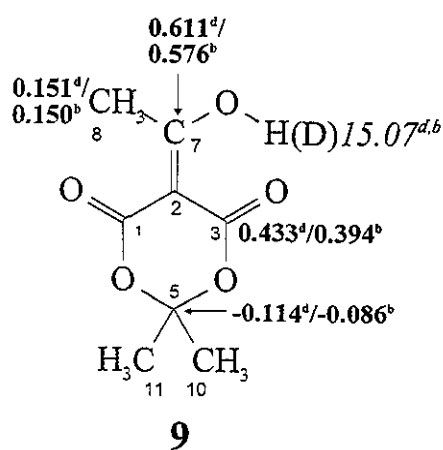
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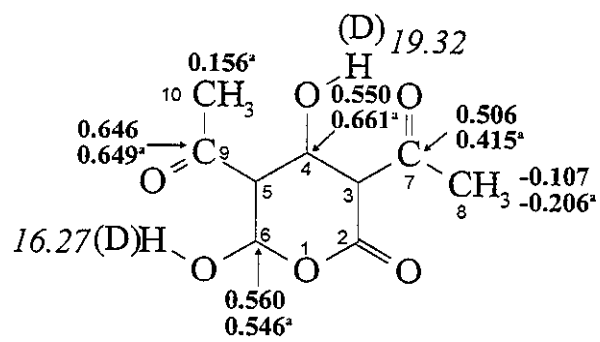


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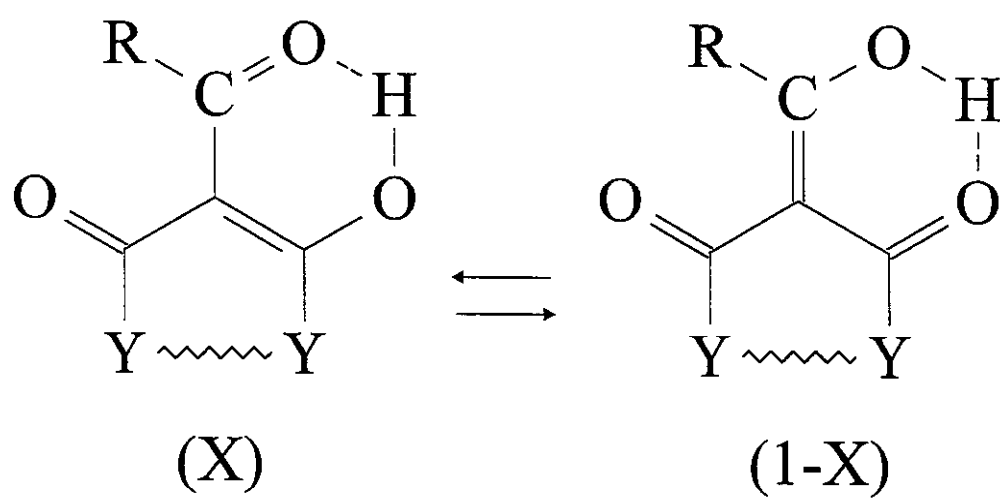


8





17



Y = C, O or N

R = H, Me, Et, iPr, t-Bu, Ph-CH₂- or 4-NO₂-C₆H₄

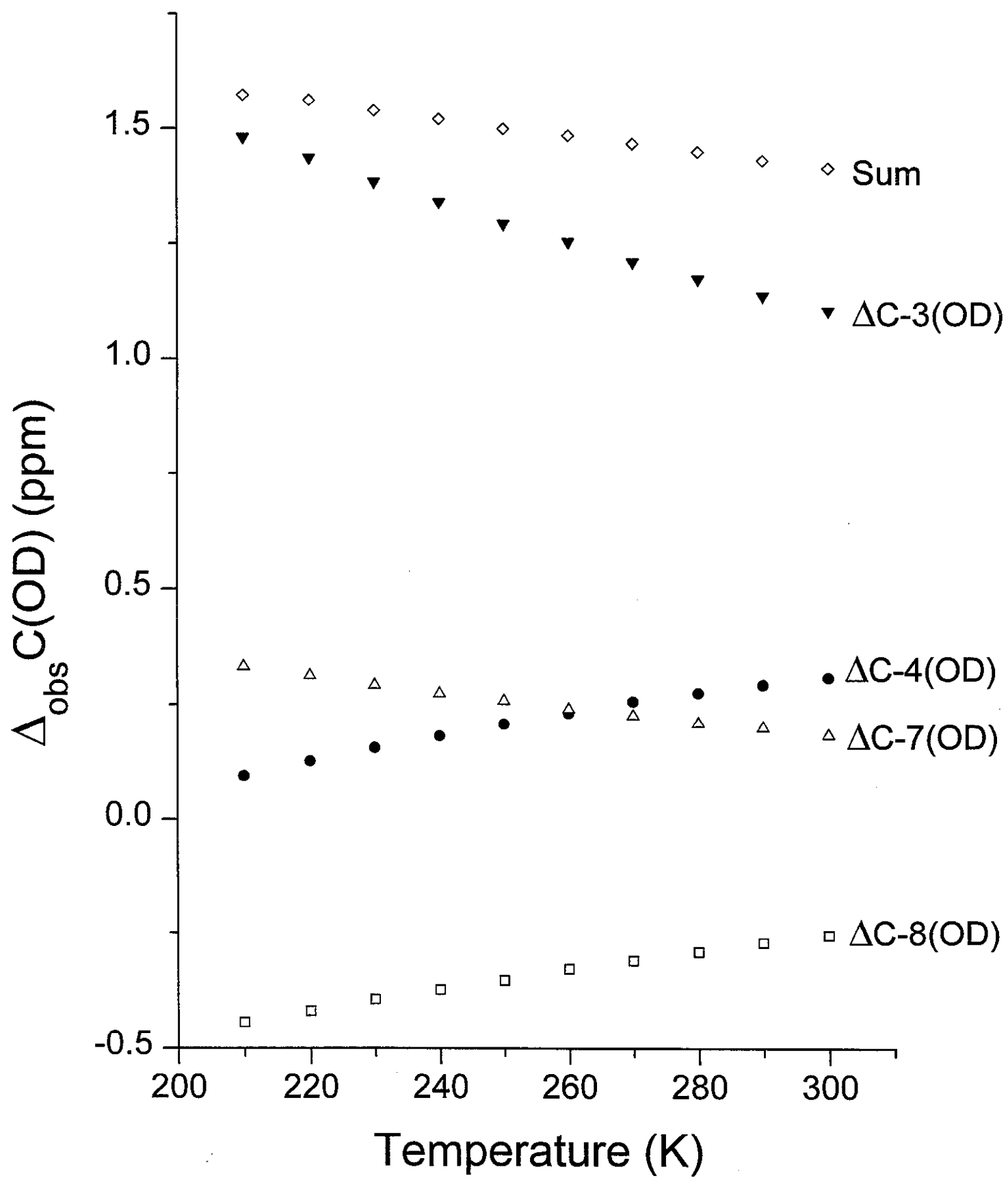


Fig. 2

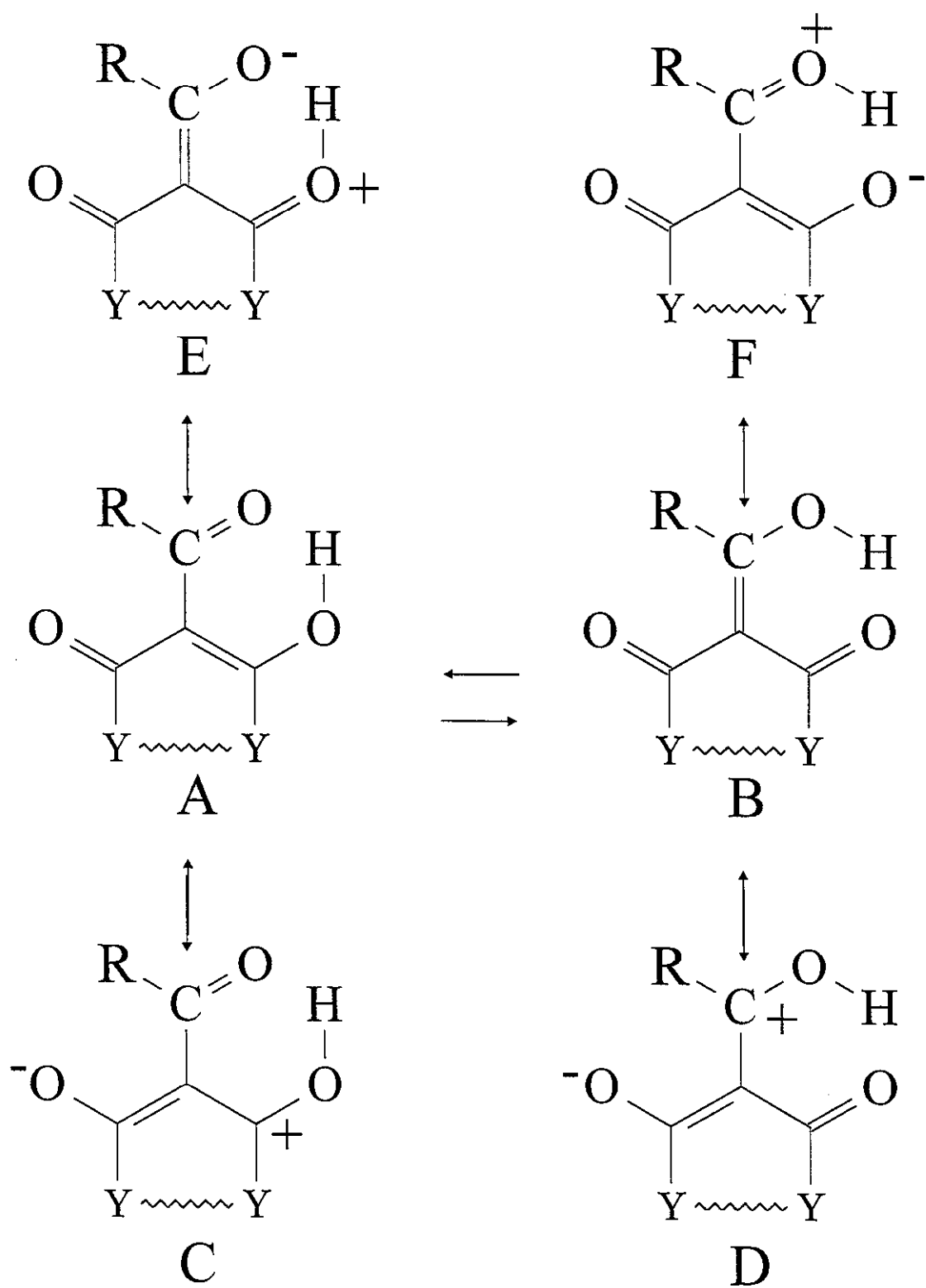


Fig. 3

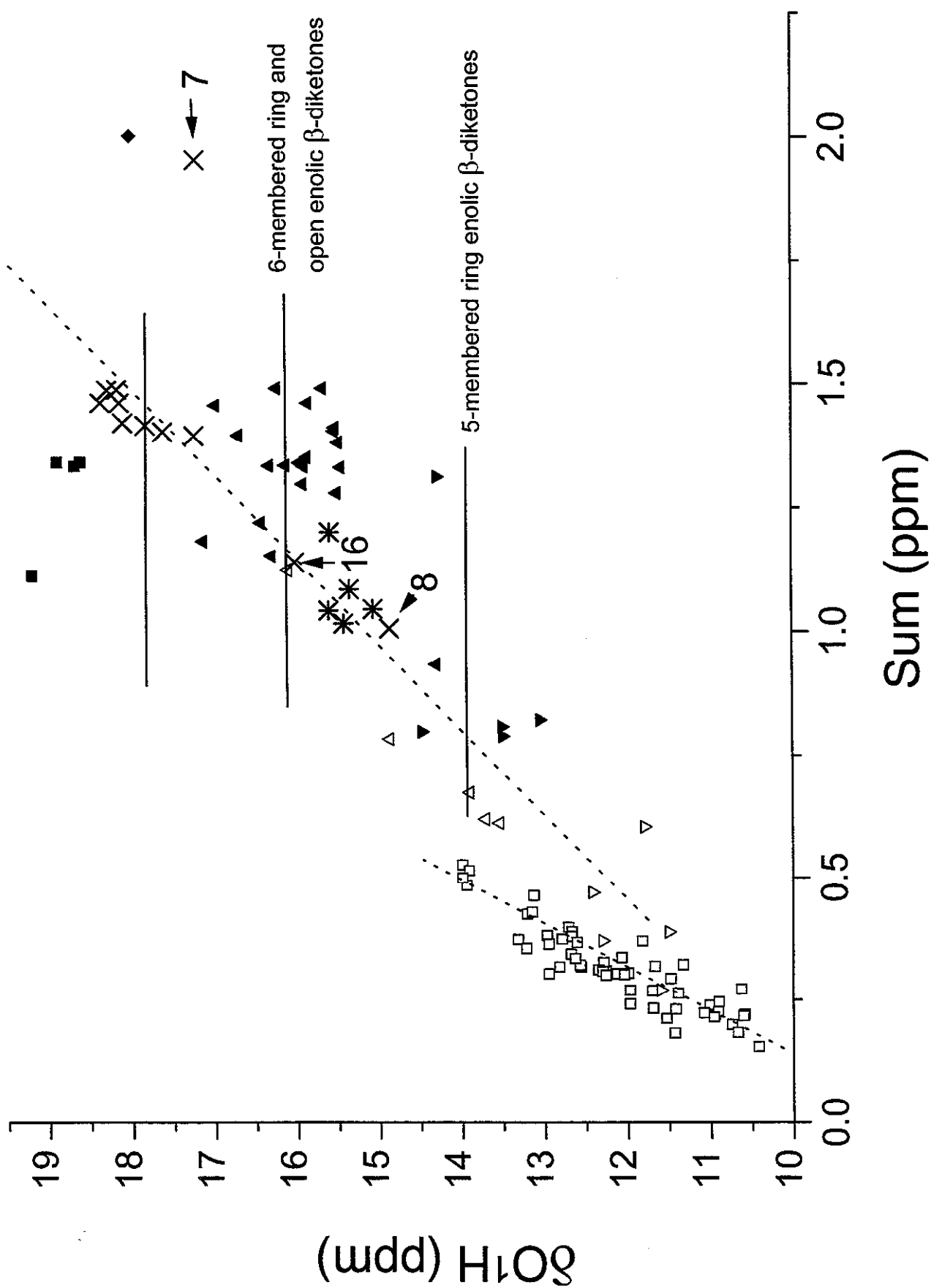


Fig. 4

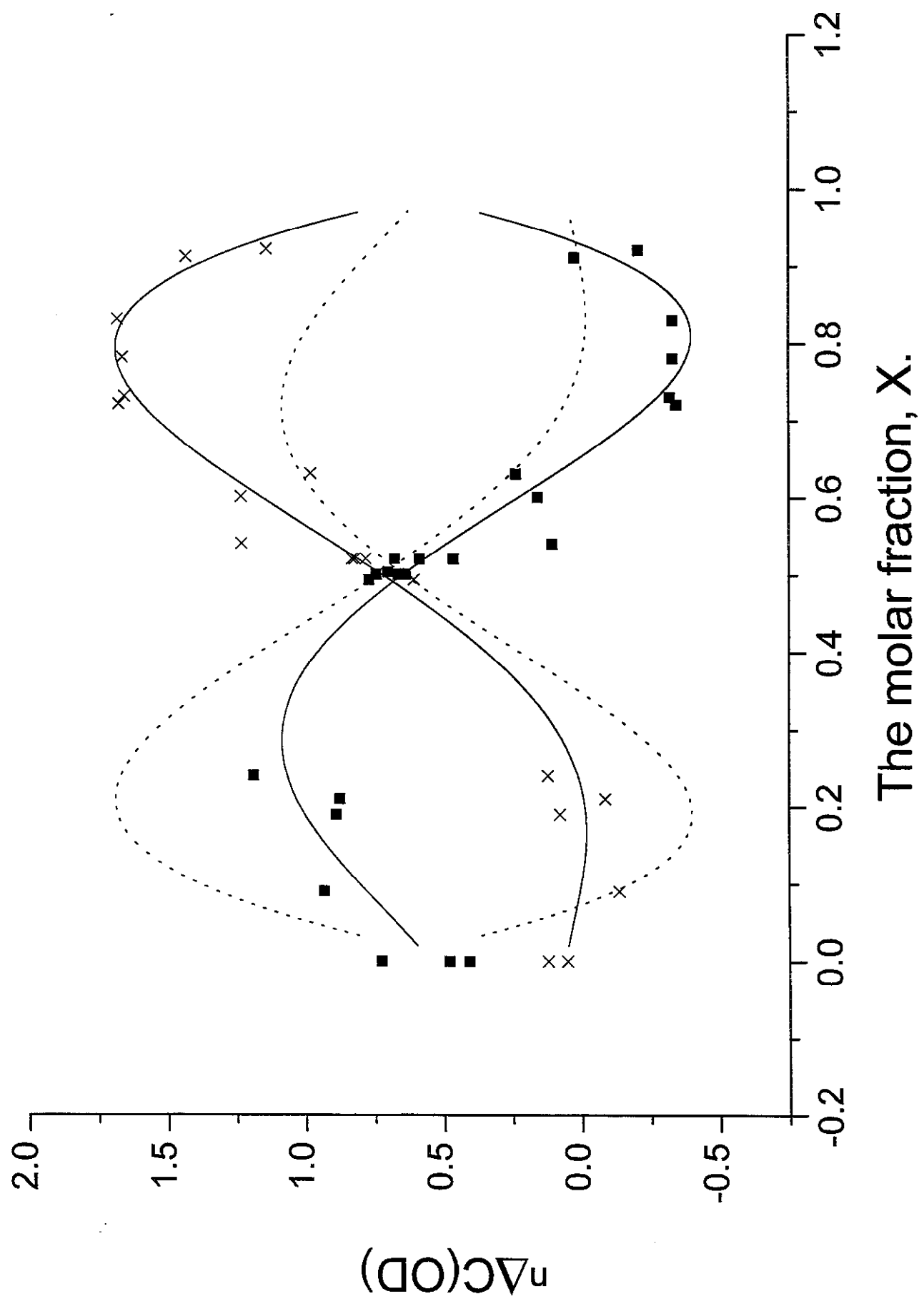


Fig. 5